FORTOVASE®
saquinavir

Releasing the Power of Saquinavir

Product Monograph

Contents

Introduction

Human immunodeficiency virus (HIV) disease was first described in 1981. The rapid spread of the virus since then has been countered by vigorous research and development programmes from the scientific community, resulting in major advances in antiretroviral therapeutics.

Until recently, nucleoside analogues were the only class of antiviral agents available for the management of HIV disease. However, in December 1995, Invirase®, a hard gelatin capsule formulation of saquinavir mesylate was licensed in the USA, providing a new option for the treatment of HIV. Saquinavir is the product of rational drug design and was the first of a new class of antiretroviral agents, the HIV protease inhibitors. These latter agents inhibit viral replication by preventing the cleavage of the HIV gag and gag-pol polyproteins, a step that is essential for the formation of mature viral particles. In clinical trials, Invirase has been shown to significantly improve virological and immunological markers of HIV disease, to delay the onset of AIDS-defining illness and to prolong survival. It acts synergistically when used in combination with nucleoside analogues and has an excellent safety profile. Experience with Invirase has shown that resistance to saquinavir develops at a low frequency. The initial resistance profile of saquinavir is unique and does not appear in persons not treated with protease inhibitors prior to saquinavir. Therefore, the majority of individuals initiating therapy with a regimen containing saquinavir will benefit. In addition, the unique initial profile means that if treatment is switched to another protease inhibitor in a timely fashion after failure of saquinavir therapy, the majority of recipients can achieve benefit.

Data indicate that the extent of the clinical benefit provided by saquinavir is related to plasma concentration of the drug. A new, soft gelatin capsule formulation of saquinavir (Fortovase®) is now available; it delivers plasma concentrations that are significantly greater than those achieved with Invirase. Data from clinical trials indicate that the enhanced plasma exposure provided by Fortovase translates into more potent antiviral activity, while still maintaining a good tolerability profile.

The use of Fortovase in combination with other antiretroviral agents offers a new dimension to therapy for individuals with HIV infection and AIDS.

Invirase has been shown to significantly improve virological and immunological markers of HIV disease, to delay the onset of AIDS-defining illness and to prolong survival

The enhanced plasma exposure provided by Fortovase translates into more potent antiviral activity, while still maintaining a good tolerability profile

Saquinavir: design concept and mode of action

The main aims in the design of any antiviral agent are to identify particular molecular pathways that are unique to the virus and then to design drugs that interfere with those pathways without causing unwanted effects on the host's cellular mechanisms. A detailed biochemical understanding of the HIV–host relationship is therefore critical for the design of antiretroviral agents and has revealed several potential targets for new drugs.

Intracellular targets for anti-HIV agents

There are several stages in the replication cycle of HIV that are suitable targets for antiviral drugs (fig. 1.1):

- at cellular attachment or penetration, when the viral envelope glycoprotein gp120 interacts with cell surface molecules such as CD4 receptors or the chemokine coreceptors
- during the transcription of viral RNA and its subsequent integration into host DNA, for which the viral reverse transcriptase and integrase enzymes, respectively, are crucial
- during the synthesis of viral mRNA from the integrated DNA, and its subsequent translation into viral proteins and polyproteins
- during the final maturation of polyproteins and assembly of virus particles, which requires the viral protease.

Currently, there are two major classes of antiretroviral agents:

1. Reverse transcriptase inhibitors (RTIs), which inhibit the production of viral DNA from RNA, thereby interfering with HIV replication early in its life cycle.

1 Attachment
2 Penetration
3 Uncoating
4 Reverse transcription
5 Integration
6 Transcription
7 RNA processing
8 Translation
9 Assembly
10 Maturation
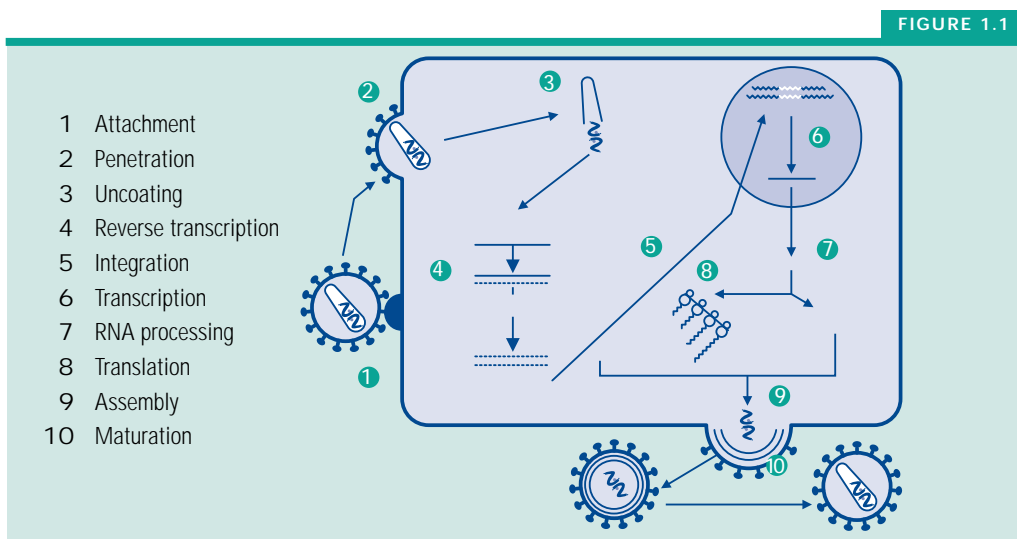
Stages in the human immunodeficiency virus (HIV) life cycle that are potential antiviral molecular targets (reprinted with permission from Expert Opin Invest Drugs; © Ashley Publications Ltd [1]).

As nucleoside analogues closely resemble human cellular metabolites, they are associated with a number of untoward effects

2. Protease inhibitors, which inhibit the much later stages of protein maturation and assembly.

Saquinavir is a protease inhibitor and was the first of this new class of agents to gain a licence for the treatment of HIV infection from the US Food and Drug Administration (FDA).

Limitations of RTIs

Several RTIs are available for treatment of HIV infection. They are divided into two classes: nucleoside analogues (NRTIs) and non-nucleoside analogues (NNRTIs). Through differing mechanisms, both classes inhibit the enzyme reverse transcriptase, thus preventing HIV from forming proviral DNA at the beginning of its replication cycle. Nucleoside analogues, especially when used in combination, have been shown to achieve reductions in plasma viraemia and improvements in survival, and to delay clinical disease progression in individuals with AIDS and HIV infection.[2–4] Greater suppression of HIV load would be expected using three or more agents in combination. However, the number of RTIs that can be included in a single regimen is restricted by several limitations intrinsic to this class of agents.

1. Since they all work at an early stage of the replication cycle, they are ineffective in chronically infected cells.[5]
2. The gene encoding HIV reverse transcriptase can undergo mutation and so become resistant to the effects of individual agents designed to inhibit this enzyme.[6] In particular, there is extensive cross-resistance between the non-nucleoside RTIs.
3. As the structure of nucleoside analogues closely resembles human cellular metabolites, they are associated with a number of clinically significant unwanted effects, such as bone marrow toxicity (e.g. zidovudine (ZDV)) and peripheral neuropathy (e.g. didanosine (ddl), stavudine (d4T), lamivudine (3TC) and zalcitabine (ddC)).
4. All nucleoside analogues must be phosphorylated to their active triphosphate forms. Competition between agents from the same nucleotide base can therefore lead to significant reductions in nucleoside triphosphate levels and consequent reduction in clinical activity.[6,7]

It is therefore unlikely that more complete control of HIV will be achieved using a combination of agents that target the same enzyme (convergent therapy). These limitations have increased the need for new classes of antiviral agents for the treatment of HIV infection.

'[T]here exists an urgent need for new antiretroviral agents with both greater and more prolonged activity, and better long-term tolerability which can more potently control viral replication, delay the emergence of resistance and, ultimately, improve clinical outcome'.[6]

Design concept for saquinavir

Saquinavir is a product of rational drug design. It is a specific inhibitor of HIV aspartic protease, a viral enzyme that is crucial for the latter stages of HIV replication.

The HIV protease enzyme was first suggested as a target for AIDS therapy in 1986.[8] Its importance for HIV infectivity was illustrated in a later *in vitro* study which showed that a single mutation eliminating HIV protease activity blocked viral infectivity.[9] From this, it was clear that a compound capable of inactivating HIV protease would be valuable in the treatment of HIV disease.

In order to avoid effects on similar host cell processes, a new agent must also display high specificity for its target enzyme. The HIV protease is a homodimeric aspartic protease, with a structure that differs from the single-chain human aspartic proteases.[6] In addition, three of the specific cleavage sites of HIV protease lie between phenylalanine and proline bonds. Cleavage of these bonds is unusual and is only effected by HIV proteases and other closely related viral proteases.[5]

The design of an HIV protease inhibitor by F. Hoffmann-La Roche was based upon these findings. Research centred on compounds that were transitional-state mimetics of the phenylalanine–proline bond, i.e. those bearing structural similarities to the enzyme target site.[5]

In late 1989, a compound that showed a high level of antiviral activity and low cellular toxicity in laboratory tests was isolated. Based on these promising findings, the compound, saquinavir, entered the development pipeline and passed from preclinical evaluation and formulation, through animal toxicity studies and evaluation in healthy volunteers, and into clinical trials in HIV-infected adults. This culminated in December 1995 with Invirase, a hard gelatin capsule formulation of saquinavir mesylate, being granted regulatory approval by the FDA for the treatment of HIV infection.

Mode of action of saquinavir

The later stages of the HIV replication cycle involve the assembly of viral components into virions, maturation into infectious particles and final exit from the host cell by a process termed 'budding' (fig. 1.2). HIV protease plays a critical role late in virion assembly; without it, new virions form – although these are not infectious.[10]

New virus particles are formed from HIV gag-pol precursor molecules, which are specifically cleaved by the HIV protease to produce essential viral enzymes and structural proteins. In the absence of a functional protease, the core of the virus fails to form.

Saquinavir was designed to specifically bind the active site of the protease. This prevents the protease from recognising and binding the HIV gag-pol polyprotein, so cleavage to the individual, essential proteins does not occur. The result is the production of new, but non-infectious, virions.

Antiviral properties of saquinavir

The antiviral effects of saquinavir were studied *in vitro* and are summarised in table 1.1. These studies have shown saquinavir to be a potent and selective inhibitor of HIV-1 and HIV-2 protease; they also indicate that, *in vitro*, it is the most potent protease inhibitor developed to date (table 1.2).

Saquinavir has an IC_{50} of approximately 2–7 nmol/L against HIV-1 and has inhibitory effects in both acute and chronically infected cells.[6] It has also been shown to be active against several ZDV-resistant strains of HIV-1.[11]

The affinity of saquinavir for human proteases is 50 000-fold lower than for HIV proteases. This high specificity for HIV protease confers high antiviral potency and low toxicity.

As well as infecting CD4 lymphocytes, HIV is known to infect several other classes of cell. Of these, cells of the monocyte lineage are important since they may contribute to the pathology of the disease and act as reservoirs for latent virus. Data obtained

HIV protease plays a critical role late in virion assembly

Saquinavir inhibits protease-mediated cleavage of the gag-pol polyprotein, producing non-infectious virions

The affinity of saquinavir for human proteases is 50 000-fold lower than for HIV proteases; this high specificity for HIV protease confers high antiviral potency and low toxicity
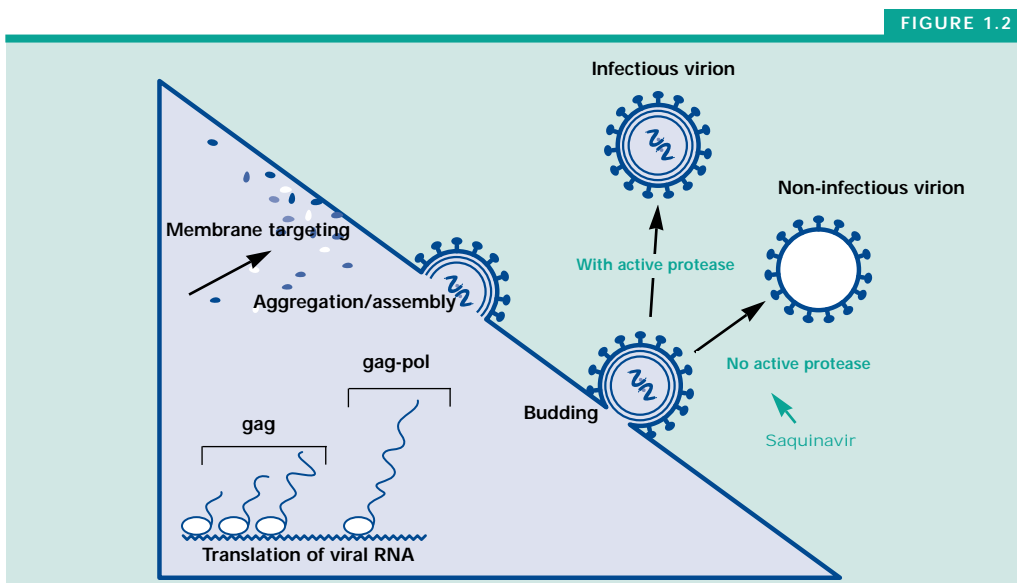
FIGURE 1.2

Final assembly and budding in the human immunodeficiency virus (HIV) replication cycle (reproduced with kind permission from Kluwer Academic Publishers[10]).

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TABLE 1.1
▶ Potent and selective inhibitor of HIV-1 and HIV-2 protease
▶ Active in resting cells
▶ Active in T cells and monocytes
▶ Effective against zidovudine-resistant strains
▶ Acts synergistically with nucleoside analogues

Abbreviation: HIV = human immunodeficiency virus.

In vitro *antiviral properties of saquinavir*

Saquinavir, unlike nucleoside analogues, does not require metabolic activation, extending its activity into resting cells

using an *in vitro* model of monocyte infection indicate that saquinavir inhibits HIV protease in monocytic cells. In a chronically HIV-infected promonocytic cell line, both morphological maturation of virions and enzymic processing of the gag polyprotein were inhibited by nanomolar concentrations of saquinavir.[12] In addition, saquinavir, unlike nucleoside analogues, does not require metabolic activation. This extends its activity into resting cells.

In vitro *antiviral inhibitory concentrations of human immunodeficiency virus protease inhibitors (reproduced with permission)* [6]

TABLE 1.2		
Drug	**IC_{50} (nmol/L)**	**IC_{90} (nmol/L)**
Saquinavir	3.5	50
Indinavir	–	≤100[a]
Ritonavir	27	90
Nelfinavir	22	60[a]
Amprenavir (VX-478; 141W94)	10	80

[a] IC_{95}.

Benefits of combination therapy

The potential value of combination chemotherapy with saquinavir and nucleoside analogues has been demonstrated in several studies.[12] Combinations of saquinavir with ZDV and with ddC clearly produce synergistic antiviral activity *in vitro*, with no evidence of increased cytotoxicity.

2 Clinical pharmacokinetics of Fortovase

Saquinavir was initially formulated as Invirase, a hard gelatin capsule containing the drug as the mesylate salt. More recently, a new soft gelatin capsule formulation of saquinavir as a free base, Fortovase, has been developed. At the recommended dosage, this formulation achieves plasma saquinavir concentrations approximately 8-fold greater than those attained with Invirase.

Absorption and plasma exposure

The absorption and bioavailability of Fortovase has been investigated in an open-label phase I/II study (NV15107) in 88 HIV-infected persons. Participants were randomised to receive either Invirase 600 mg (n=11) or Fortovase 400 mg (n=12), 800 mg (n=33) or 1200 mg (n=32) every 8 hours for 8 weeks.

For patients treated with Fortovase (1200 mg tid) the mean plasma concentrations of saquinavir remained substantially above the usually observed IC_{90} value (5–80 nmol/L depending on cell line) for the whole dosage interval. The exposure level achieved with Fortovase was considerably greater than that achieved with Invirase. The steady-state area under the plasma concentration–time curve (AUC) over 8 hours among participants receiving Fortovase 1200 mg for 3 weeks was approximately 8-fold greater than that among those receiving Invirase 600 mg (7.25 vs 0.87 µg·hour·ml⁻¹).[1] Increasing the dosage of Fortovase resulted in a greater than proportional increase in drug exposure; tripling the dosage from 400 to 1200 mg tid produced an 8-fold increase in AUC_{0-8} (fig. 2.1). This study established 1200 mg tid as the recommended dosage of Fortovase using exposure–response modelling techniques.[2]

Comparison of pharmacokinetic parameters between single- and multiple-dose studies in healthy volunteers indicates that the steady-state plasma AUC following multiple doses of Fortovase 1200 mg tid (n=18) is approximately 80% (95% CI: 22–176%) greater than that attained following a single

1200 mg dose (n=30). Interestingly, when this dosage was given to HIV-infected persons, both the AUC and maximum plasma concentrations (C_{max}) of saquinavir were approximately double those observed in healthy volunteers (8.84 vs 4.16 µg·hour·ml⁻¹, and 2.48 vs 1.42 µg/ml, respectively).[1]

Food greatly enhances the absorption of Fortovase. In healthy volunteers, the mean 12-hour AUC following a single 800 mg dose was over 6-fold greater when taken with breakfast (protein 48 g, carbohydrate 60 g, fat 57 g; 1006 kcal) than when taken under fasting conditions (study protocol WK15054, data on file, Roche Products Ltd) (fig. 2.2).[1] Preliminary results have suggested that plasma concentrations of saquinavir were

Mean steady-state saquinavir plasma concentration (area under concentration–time (AUC) curve over 8 hours) in human immunodeficiency virus (HIV)-infected subjects.[1]
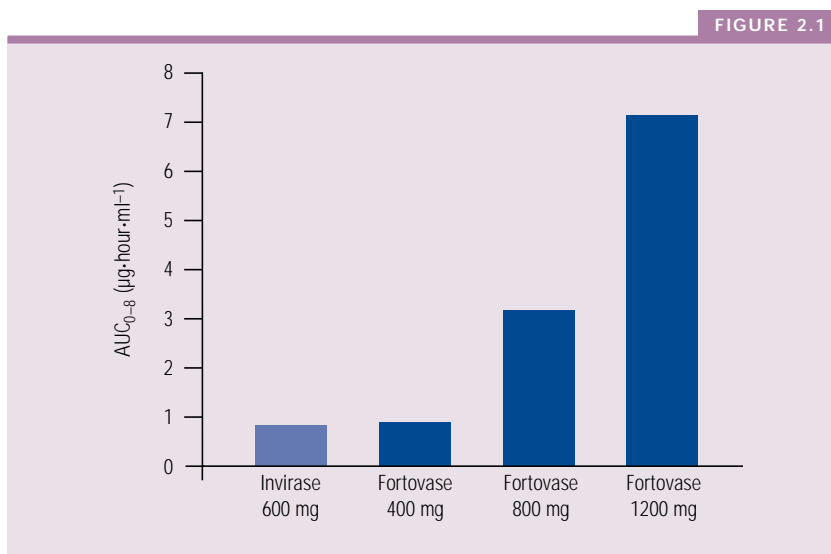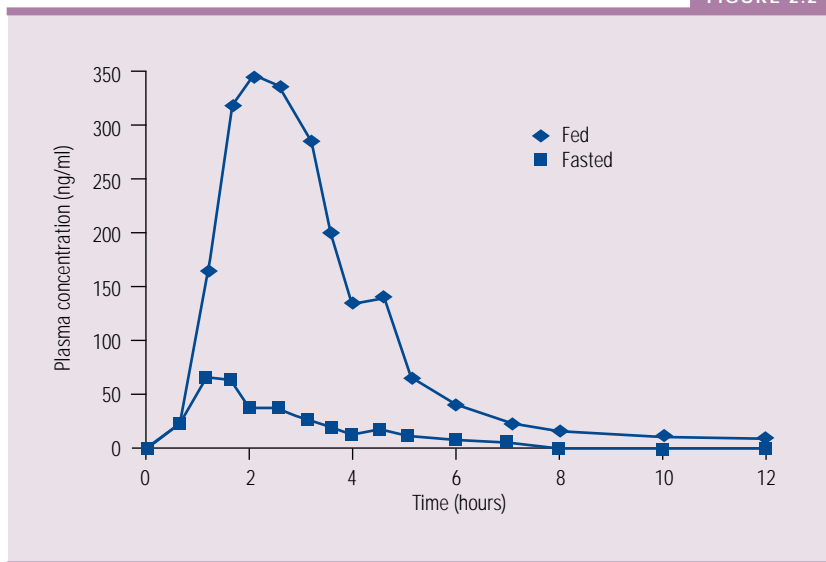

FIGURE 2.1

13

FIGURE 2.2

Plasma concentration of saquinavir following a single dose of Fortovase 800 mg in 12 healthy male volunteers in fed (1006 kcal) and fasted states.[1]

Food greatly enhances the absorption of Fortovase

There were no significant differences in pharmacokinetic parameters between men and women

The impact of renal impairment on saquinavir elimination should be minimal

approximately 50% lower when the drug was administered with a light breakfast than with a heavy breakfast.[3]

The mean steady-state volume of distribution following intravenous saquinavir 12 mg was 700 L, indicating that saquinavir partitions into the tissues. At plasma concentrations of up to 30 µg/ml, approximately 97% of the circulating drug is bound to plasma proteins.[1] Because of this high degree of protein binding, levels of saquinavir in the cerebrospinal fluid (CSF) are low in comparison with plasma levels. However, this does not mean that saquinavir does not reach brain tissue; indeed, animal studies suggest that levels of saquinavir in brain tissue are several times higher than in the CSF (data on file, Roche Products Ltd).

In a study of 30 healthy volunteers who received a single dose of Fortovase 1200 mg, there were no significant differences in pharmacokinetic parameters between men and women.[1]

Metabolism and elimination

In vitro studies have shown that the metabolism of saquinavir is primarily mediated by cytochrome P450, with isoenzyme CYP3A4 responsible for more than 90% of hepatic metabolism. Following oral admin-

istration, saquinavir undergoes extensive first-pass metabolism to a range of inactive mono- and di-hydroxylated metabolites.[1]

Systemic clearance of saquinavir is rapid; the mean residence time of the drug after intravenous doses of 6, 36 and 72 mg was 7 hours (n=8).[1] Elimination of saquinavir is predominantly non-renal. In a mass balance study of orally administered ^{14}C-saquinavir 600 mg (n=8), approximately 88% of the radiolabel was recovered in the faeces, with only 1% being excreted in the urine.[1] The impact of renal impairment on saquinavir elimination should therefore be minimal.

Drug interactions

Several drug-interaction studies have been performed with both the hard and soft gel formulations of saquinavir; these have indicated that saquinavir has a low potential for adverse drug interactions. It is important to note that observations with one formulation may not necessarily be predictive of those with the other.

The plasma concentrations of the nucleoside analogues ddC and ZDV are not significantly affected by concomitant intake of Invirase. Similarly, neither of these nucleoside analogues themselves influence saquinavir plasma levels.

As with other protease inhibitors, saquinavir undergoes hepatic metabolism, and concomitant administration of agents that inhibit or induce hepatic enzymes will affect plasma saquinavir concentrations. For example, other protease inhibitors such as ritonavir,[1] nelfinavir[1,4,5] and indinavir[1,6] inhibit the action of CYP3A4, and their coadministration with Fortovase results in significantly elevated saquinavir plasma levels (table 2.1). However, Fortovase appears to have no relevant effect on the plasma concentration of nelfinavir or ritonavir (effect on indinavir has not been formally tested, but no major interaction has been observed; table 2.2). These *in vivo* synergies between saquinavir and other protease inhibitors are being evaluated in clinical trials, which may identify potent new combination regimens for treating HIV infection (see chapter 3, page 17).

TABLE 2.1

Coadministered drug	Saquinavir dose	No. of participants	Change in saquinavir AUC (95% CI)	Change in saquinavir C_{max} (95% CI)
Indinavir 800 mg q8h × 2 days	Fortovase 800 mg × 1 dose 1200 mg × 1 dose	6 volunteers 6 volunteers	↑ 620% (273–1288%) ↑ 364% (190–644%)	↑ 551% (320–908%) ↑ 299% (138–568%)
Nelfinavir 750 mg × 4 days	Fortovase 1200 mg × 1 dose	14 patients	↑ 392% (271–553%)	↑ 179% (105–280%)
Ritonavir[a] 200 mg bid × 14 days 300 mg bid × 14 days 400 mg bid × 14 days	Fortovase 800 mg bid × 14 days	8 volunteers	↑ 1589% (862–2867%) ↑ 1981% (1098–3513%) ↑ 2158% (1193–3842%)	↑ 757% (416–1325%) ↑ 989% (562–1690%) ↑ 857% (479–1481%)
Clarithromycin 500 mg bid × 7 days	Fortovase 1200 mg tid × 7 days	12 volunteers	↑ 177% (108–269%)	↑ 187% (105–300%)
Zalcitabine 0.75 mg tid × 7 days	Invirase 600 mg tid × 7 days	27 patients	–	–
Zidovudine 200 mg tid × >7 days	Invirase 600 mg tid × >7 days	20 patients	–	–
Ritonavir 400 mg bid steady state[a]	Invirase 400 mg bid steady state	7 patients	↑ 1587% (808–3034%)[c]	↑ 1277% (577–2702%)[c]
Delavirdine 400 mg × 14 days	Invirase 600 mg tid × 21 days	13 volunteers	↑ 348% (192–587%)	↑ 317% (165–556%)
Nevirapine 200 mg bid × 21 days	Invirase 600 mg tid × 7 days	23 patients	↓ 24% (1–42%)	↓ 28% (1–47%)
Ketoconazole 200 mg qd × 6 days	Invirase 600 mg tid × 6 days	12 volunteers	↑ 130% (58–235%)	↑ 147% (53–298%)
Ranitidine 150 mg × 2 doses	Invirase 600 mg tid × 1 dose	12 volunteers	–	↑ 74% (16–161%)
Rifabutin 300 mg qd × 14 days	Invirase 600 mg tid × 14 days	12 patients	↓ 43% (29–53%)	–
Rifampicin 600 mg qd × 7 days	Invirase 600 mg tid × 14 days	12 volunteers	↓ 84% (79–88%)	↓79% (68–86%)

[a] The absolute plasma exposures when ritonavir was combined with identical doses of either Invirase or Fortovase were not significantly different (AUC_{0-12} 18.2 and 20.0 µg·hour·ml⁻¹, respectively).
[b] Relative to the typical exposure observed following the standard Fortovase 1200 mg tid regimen (n=33).
[c] Relative to the typical exposure observed following the standard Invirase 600 mg tid regimen (n=114).

Abbreviations and symbols: AUC = area under plasma concentration–time curve; CI = confidence interval; C_{max} = maximum plasma concentration; ND = not determined; qd = every day; q8h = every 8 hours; ↑ = increase; ↓ = decrease; – = no relevant change observed.

Effect of coadministered drugs on plasma saquinavir levels [1,7]

				TABLE 2.2
Coadministered drug	Saquinavir dose	No. of participants	Change in coadministered drug AUC (95% CI)	Change in coadministered drug C_{max} (95% CI)
Clarithromycin 500 mg bid × 7 days	Fortovase 1200 mg tid × 7 days	12 volunteers	↑ 45% (17–81%)	↑ 39% (10–76%)
Nelfinavir 750 mg × 1 dose	Fortovase 1200 mg tid × 4 days	14 patients	↑ 18% (5–33%)	–
Ritonavir 400 mg bid × 14 days	Fortovase 400 mg bid × 14 days	8 volunteers	–	–
Terfenadine 60 mg bid × 11 days	Fortovase 1200 mg tid × 4 days	12 volunteers	↑ 368% (257–514%)	↑ 253% (164–373%)

Abbreviations and symbols: AUC = area under plasma concentration–time curve; CI = confidence interval; C_{max} = maximum plasma concentration; ↑ = increase; ↓ = decrease; – = no relevant change observed.

Effect of Fortovase on coadministered drug levels[1]

Studies indicate that saquinavir has a low potential for adverse drug interactions

In vivo **synergies between saquinavir and other protease inhibitors are being evaluated as potent new antiretroviral regimens**

Delavirdine, ketoconazole and ranitidine have also been shown to increase plasma saquinavir levels (data obtained with Invirase). Conversely, those drugs that induce hepatic enzymes, such as nevirapine and the antimycobacterial agents rifabutin and rifampicin, reduce saquinavir levels (data available for Invirase only).

The drugs midazolam, triazolam and ergot derivatives should be avoided with Fortovase. As with other protease inhibitors, astemizole, cisapride and terfenadine are contraindicated in persons receiving Fortovase. Fortovase is contraindicated in patients with hypersensitivity to saquinavir or to any of the other components contained in the capsule. Fortovase is contraindicated in patients receiving concomitant administration of drugs which significantly (>50%) decrease plasma levels of saquinavir, e.g. rifampicin. Fortovase is also contraindicated in patients with severe hepatic impairment.

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3 Clinical experience with Fortovase

Fortovase is indicated for use in combination with other antiretroviral agents in the treatment of HIV. This indication is based on the extensive clinical experience with the hard gelatin capsule formulation of saquinavir (Invirase) coupled with the Fortovase phase II and III trial results showing that this new soft gelatin capsule formulation provides more profound suppression of HIV RNA.

Invirase was launched in the USA in December 1995 for the treatment of HIV, and more than 138 000 persons have been treated with this drug to date. Extensive clinical experience with this formulation has shown that significant improvements in virological (plasma HIV RNA) and immunological (CD4 cell count) markers of HIV disease occur in individuals receiving saquinavir.[1–4] Furthermore, two large-scale clinical trials with Invirase have demonstrated that treatment with saquinavir in combination with RTIs significantly reduces the risk of disease progression and death in different HIV-infected patient populations.[3,4] Study NV14256 evaluated Invirase in combination with ddC in 940 persons heavily pretreated with ZDV. It was found that the relative risk of death was reduced by 72% in persons receiving Invirase plus ddC compared to those treated with ddC alone (p=0.002).[3] Study SV14604 included 3485 participants who were naïve to antiretroviral therapy or had received ZDV for <16 weeks. For the primary endpoint of progression to AIDS or death, treatment with Invirase plus ddC plus ZDV was shown to be significantly superior to ddC plus ZDV, reducing the relative risk of disease progression or death by 50% (p<0.0001).[4] Quality-of-life outcome, as measured by physical health summary scores at 48 weeks, was also significantly better in the triple-therapy group (p<0.05).[5] This was the first study to demonstrate the clinical benefit of initiating triple therapy with a protease inhibitor-containing regimen.

Data from a pilot study of Invirase at dosages of 3600 and 7200 mg/day in 40 HIV-infected adults with CD4 cell counts of 200–500 cells/mm^3 indicated the potential to increase the drug concentration to achieve greater antiviral activity, while retaining a good safety/tolerability profile.[6] With Fortovase 1200 mg, the plasma saquinavir levels achieved are approximately 8-fold higher than those attained with the recommended dosage of Invirase.[7] Based on these results, greater therapeutic efficacy was expected with Fortovase. This has been confirmed in phase II/III trials, which show that Fortovase produces profound and prolonged suppression of plasma viraemia.[8–13] Comparative studies have found that its antiviral activity, when given in combination with RTIs, is significantly superior to that of Invirase and comparable to that of indinavir.[8,10] Throughout clinical trials, Fortovase has been associated with substantial improvements in immunological markers of HIV disease (e.g. CD4 cell counts) and has proved to be exceptionally well tolerated.[10,11,13]

Dose-ranging data
As discussed in chapter 2 (page 13), study NV15107 evaluated the pharmacokinetic profile of escalating doses of Fortovase relative to that of standard-dose Invirase.[7] The study also measured changes in HIV RNA levels, enabling the exposure–response relationship to be investigated. Participants were randomised to receive either Invirase 600 mg tid (n=11) or one of three doses of Fortovase tid

The risk of death was reduced by 72% in ZDV-failed/intolerant persons receiving Invirase plus ddC compared to those treated with ddC alone (p=0.002)

In antiretroviral-naïve patients, Invirase plus ddC plus ZDV was significantly superior to ddC plus ZDV, reducing the risk of disease progression or death by 50% (p<0.0001)

The antiviral activity of Fortovase, when combined with RTIs, is significantly superior to that of Invirase

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Study NV15107 demonstrated the optimal dosage of Fortovase to be 1200 mg tid

</div>

(400 mg (n=12), 800 mg (n=33) or 1200 mg (n=32)) for 8 weeks. Plasma HIV RNA was measured at baseline and at weeks 1, 2, 3, 4 and 8, and samples for pharmacokinetic analysis were obtained after 1 and 3 weeks of treatment, immediately prior to and 1, 2, 3, 4, 6 and 8 hours after dose administration. The relationship between surrogate marker responses and saquinavir exposure (AUC_{0-24}) was investigated using an empirical modelling method. Data were fitted to six exposure–effect mathematical models of increasing complexity (three linear, three non-linear) using SAS (PROC NLIN) programmed to return the Akaike and Schwarz model selection criteria.

In total, 84 subjects were available for pharmacokinetic/pharmacodynamic evaluation. The relationship between HIV RNA and AUC_{0-24} was best described by a two-parameter E_{max} model, which predicted a maximum reduction in HIV RNA load of 1.79 log_{10} copies/ml (11% coefficient of variation) with an EC_{50} of 3.23 µg·hour·ml^{-1} (45% coefficient of variation) (fig. 3.1). This investigation demonstrated the optimal dosage of Fortovase to be 1200 mg tid. The AUC_{0-24} of Fortovase 1200 mg tid was approximately 20 µg·hour·ml^{-1}, which is nearly 6 times the EC_{50} based on HIV RNA peak reduction. This corresponds to 85% of the maximum achievable effect of saquinavir monotherapy in the group studied.

Peak viral load reduction from baseline in plasma human immunodeficiency virus (HIV) RNA vs area under the plasma–concentration curve (AUC) in patients receiving Fortovase 400 mg (n=12), 800 mg (n=33) or 1200 mg (n=32) tid for 8 weeks. Best fit of the predicted mean (solid line) ± 95% confidence band (dotted lines), as modelled by E_{max} regression.[7]

Fortovase in combination with RTIs

Protease inhibitor-based triple therapy is now considered standard of care for treatment of HIV infection. Several clinical trials were therefore designed to evaluate the activity, tolerability and safety of Fortovase in combination with two RTIs. The rationale for combining Fortovase with RTIs include:

- the two classes of agent act at different stages of the HIV life cycle and so attack the virus through two independent, critical mechanisms (divergent therapy)
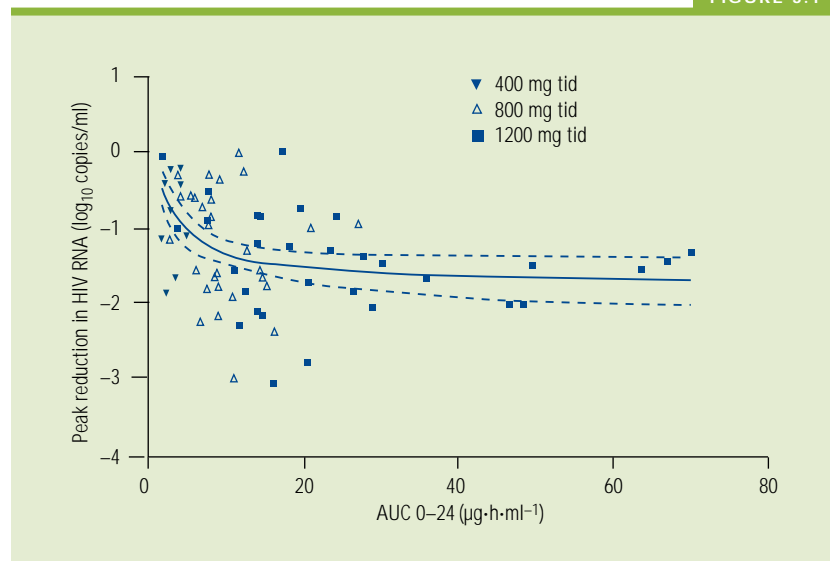- the two classes may work synergistically.

Study NV15355

The activity of Fortovase was compared with that of Invirase in study NV15355.[8] This phase III, randomised, open-label trial included 171 HIV-infected persons from 23 centres in the USA and Canada. To be eligible for inclusion, participants were to have HIV RNA levels ≥5000 copies/ml and to be antiretroviral-naïve, defined as never having received a protease inhibitor or any nucleoside analogue for more than 4 weeks, and to be free of all antiretroviral therapy for 28 days prior to screening. Participants were randomised to receive either Fortovase 1200 mg (n=90) or Invirase 600 mg (n=81) tid, each in combination with two nucleoside analogues chosen in conjunction with the physician. After 16 weeks, participants were free to cross over to the saquinavir formulation of choice for the remaining 32 weeks of the study. Baseline characteristics of the two treatment groups are summarised in table 3.1.

At the 16-week primary analysis, Fortovase was found to provide significantly superior antiviral activity compared with Invirase. At this time-point, the proportion of participants with plasma HIV RNA <400 copies/ml (Amplicor assay) was 80% (60/75) in the Fortovase arm and 43% (30/69) in the Invirase arm (p=0.001) (fig. 3.2), while the corresponding values for those with HIV RNA <50 copies/ml (UltraSensitive assay) were 46% (33/72) and 28% (19/69), respectively. The mean reductions in plasma HIV RNA from baseline (using the UltraSensitive assay for values <400 copies/ml) were 2.5 log_{10} copies/ml and 1.9 log_{10} copies/ml in

FIGURE 3.1

the Fortovase and Invirase arms, respectively. The proportion of participants with HIV RNA levels below quantification was still increasing at this time-point. CD4 counts increased by a mean of 97 cells/mm³ in the Fortovase arm and by 115 cells/mm³ in the Invirase arm.

Data are available out to 24 weeks and indicate that the HIV RNA response to therapy is maintained in individuals remaining on Fortovase (mean reduction from baseline 2.7 $\log_{10}$ copies/ml). At this time-point, plasma HIV RNA levels were <400 copies/ml in 79% of Fortovase recipients (54/68) and <50 copies/ml in 66% (44/67). This study therefore demonstrates that, when given in combination with two nucleoside analogues, Fortovase provides significantly superior suppression of plasma viraemia compared with Invirase. Full details of the comparative safety/tolerability results from this study are discussed in chapter 4 (page 24).

TABLE 3.1		
	Fortovase	**Invirase**
No. of patients (intent to treat)	90	81
Percentage of females	8	9
Mean HIV RNA ($\log_{10}$ copies/ml)	4.8	4.8
Mean CD4 cell count (cells/mm³)	448	408
Mean CD4 proportion (%)	22.1	20.9

Baseline characteristics, study NV15355 [8]

FIGURE 3.2
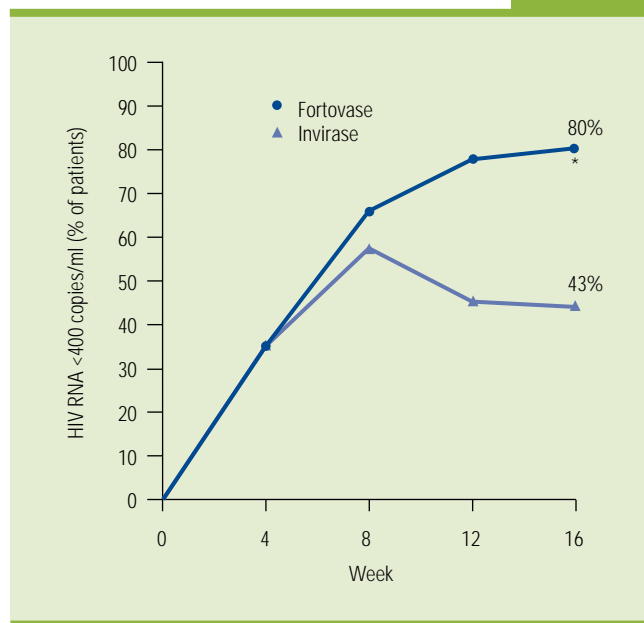
Proportion of patients with HIV RNA <400 copies/ml (Amplicor assay) after receiving two nucleoside analogues plus either Invirase 600 mg tid (n=81) or Fortovase 1200 mg tid (n=90). Baseline HIV RNA was 4.8 $\log_{10}$ copies/ml in each arm. * p=0.001 vs Invirase (study NV15355).[8]

SUN

The SUN study evaluated the efficacy of a triple combination of Fortovase 1200 mg tid plus ZDV 300 mg bid plus 3TC 150 mg bid in 42 HIV-positive antiretroviral-naïve persons with plasma HIV RNA levels >10 000 copies/ml and a CD4 count >100 cells/mm³.[9] Over the 24 weeks of the study, HIV RNA levels dropped by a mean of 3.14 $\log_{10}$ copies/ml (fig. 3.3), falling to below the limit of quantification of the Amplicor assay (400 copies/ml) in 21 (91%) of the 23 persons completing 24 weeks of therapy. Mean CD4 count increased by 184 cells/mm³, with the CD4:CD8 ratio increasing from 0.5 at baseline to 0.7 by week 24

(see fig. 3.3). Treatment was generally well tolerated, with only 2 patients withdrawing because of adverse events.

CHEESE

The combination of Fortovase, ZDV and 3TC has also been evaluated in the CHEESE study, a multi-centre, open-label pilot study being conducted in the Netherlands.[10] This is the first prospective study to directly compare the activity of two protease inhibitors as part of a triple-therapy regimen. HIV-infected adults were eligible for inclusion if:

In study NV15355, 80% of persons receiving Fortovase had 'undetectable' levels of virus (HIV RNA<400 copies/ml) at week 16

In the SUN trial, HIV RNA load fell to <400 copies/ml in 91% of participants completing 24 weeks' therapy

FIGURE 3.3
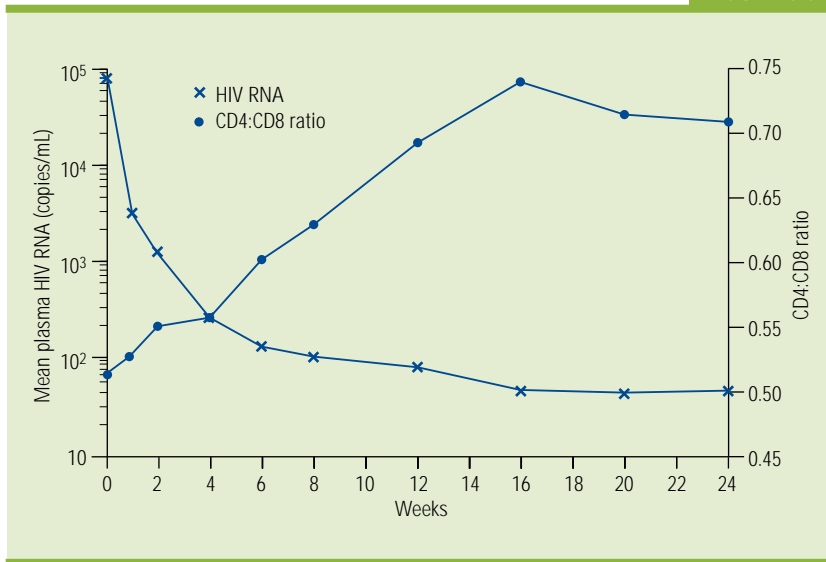
Mean plasma HIV RNA (baseline 4.8 log$_{10}$ copies/ml) and CD4:CD8 ratio (baseline 419 cells/mm³) in 42 patients receiving Fortovase 1200 mg tid plus zidovudine 300 mg bid plus 3TC 150 mg bid for 24 weeks (n=23 at week 24) (SUN study).[9]

In CHEESE, HIV RNA load fell to <400 copies/ml in both the Fortovase and indinavir groups by week 8 and remained below this level to week 24

In contrast with indinavir, Fortovase was associated with a substantial increase in mean CD4 cell count over 24 weeks

- they had received no prior antiretroviral therapy or had received ZDV for <12 months
- they had received no prior treatment with protease inhibitors or 3TC
- they had HIV RNA ≥10 000 copies/ml and/or CD4 count <500 cells/mm³ and/or HIV-related signs or symptoms according to 1993 Centers for Disease Control (CDC) B or C definitions.

A total of 63 persons were included and randomised to receive ZDV 200 mg tid plus 3TC 150 mg bid, plus either Fortovase 1200 mg tid (n=30) or indinavir 800 mg q8h (n=33) for 48 weeks. After 16 weeks, participants were permitted to enter a roll-over study in case of virological failure. The study is still ongoing, and 24-week data are available to date.

At baseline, mean HIV RNA loads were 4.9 and 5.0 log$_{10}$ copies/ml in the Fortovase and indinavir groups, respectively, and mean CD4 cell counts were 301 and 337 cells/mm³, respectively. Two participants in the Fortovase group and one in the indinavir group had received previous treatment with ZDV. As can be seen from figure 3.4, both regimens were highly effective in reducing viral load. By week 12, mean viral load had fallen to <400 copies/ml (Amplicor assay) in both groups, representing a reduction of 2.3 log$_{10}$ copies/ml from baseline.

Preliminary data indicate that this virological response is sustained out to 24 weeks. In contrast to indinavir, Fortovase was also associated with a substantial increase in mean CD4 cell count over 24 weeks (see fig. 3.4). Both regimens were generally well tolerated. Four Fortovase recipients and 7 indinavir recipients withdrew prematurely from the study.

NV15182

The large safety study NV15182 also yielded data supporting the efficacy of Fortovase in combination with RTIs.[11] The primary aim of this open-label, multicentre study was to gather safety information on Fortovase 1200 mg tid over 48 weeks. In addition to Fortovase, participants took one or more RTIs of choice, and these could be changed throughout the study. As there were no study entry restrictions with regard to plasma HIV RNA levels, CD4 cell count or previous antiretroviral treatment, a very heterogeneous study population was recruited.

A total of 442 persons (mean baseline HIV RNA 4.1 log$_{10}$ copies/ml and CD4 count of 227 cells/mm³) were enrolled. Of these, 96% had received previous antiretroviral therapy for a mean of 3.9 years, and 18% had been previously treated with a protease inhibitor (usually Invirase) for a mean of 1 year.

At week 24, the reduction in plasma HIV RNA from baseline was 0.9 log$_{10}$ copies/ml and 43% of participants had unquantifiable HIV RNA levels (<400 copies/ml). As the study population was very heterogeneous, several subgroup efficacy analyses were performed. Considerably greater antiviral response was noted in the 18 individuals who were antiretroviral-naïve at baseline. In this subgroup the mean plasma HIV RNA change from baseline was –1.8 log$_{10}$ copies/ml, and 75% of participants had plasma HIV RNA levels <400 copies/ml.

Study NV15182 was initiated before the current guidelines were issued, which recommend starting new concomitant RTIs when adding or changing

FIGURE 3.4
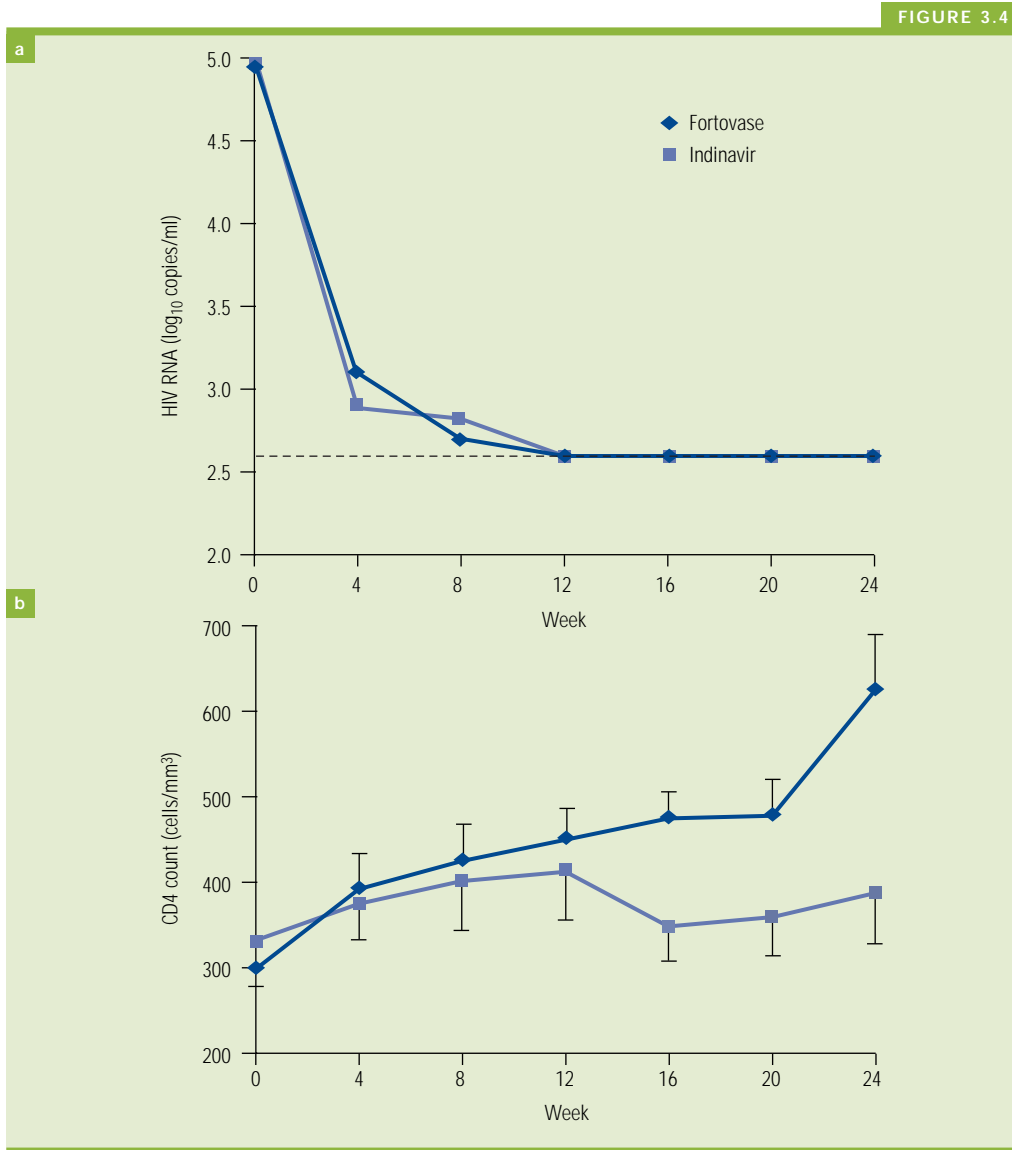
Median viral load (a) and mean CD4 count (± SEM) (b) in patients receiving zidovudine 200 mg tid plus 3TC 150 mg bid plus either Fortovase 1200 mg tid (n=30) or indinavir 800 mg q8h (n=33) (dotted line represents the limit of quantification of the Amplicor assay) (CHEESE study).[10]

protease inhibitors. Thus, the majority of participants in NV15182 added Fortovase to their existing regimens. This study supports the new guidelines by confirming a clear benefit from adding at least one new RTI simultaneously when starting Fortovase. The mean changes in plasma HIV RNA were -1.26 and -1.32 log_{10} copies/ml, respectively, in the 39 individuals starting at least one new RTI and the 18 starting at least two new RTIs (and available for the 24-week assessment). The propor-

tions of participants with plasma HIV RNA levels <400 copies/ml were 44% and 50%, respectively.

In addition to reducing CD4 cell numbers, HIV disease frequently results in an increased CD8 count and a rise in the number of activated CD8 cells. Data indicate that as well as reducing HIV viraemia, combination therapy containing Fortovase may lead to a normalisation of these T-cell phenotypes. In one study, 23 protease inhibitor-naïve

persons received Fortovase together with either ZDV plus 3TC (n=17), d4T plus 3TC (n=2) or ZDV plus ddC (n=4).[14] At baseline, mean HIV RNA level was 4.6 $\log_{10}$ copies/ml and mean CD4 count was 316 cells/mm³. By week 8, CD4 proportion had increased from 19% to 23% (p<0.001); it continued to improve to 29% (p<0.01) by week 48. The CD8 proportion fell from 61% at baseline to 51% at week 48 (p<0.002) and the proportion of CD8 cells that were activated, as measured by surface HLA-DR expression, had also fallen from a baseline value of 38% to 23% at week 36 (p<0.0003). These data suggest that Fortovase-based triple regimens might be beneficial in the restoration of disrupted T-cell phenotypes in HIV infection.

Fortovase in combination with other protease inhibitors

Attention has focused recently on the use of two protease inhibitors in combination. This strategy is supported by evidence from *in vitro* studies showing that two protease inhibitors are more effective than a single one in suppressing viral replication and delaying the emergence of resistance.[15] Furthermore, saquinavir, as with other protease inhibitors, undergoes hepatic metabolism, primarily through the cytochrome P450 system. Hence, co-administration of other protease inhibitors that inhibit the action of these enzymes (e.g. ritonavir or nelfinavir) significantly elevates saquinavir plasma levels. This synergy between protease inhibitors is being exploited in clinical trials.

Combination with nelfinavir

Data from two recent clinical studies indicate that the combination of Fortovase plus nelfinavir provides potent and durable activity against HIV while retaining the good tolerability profile of the individual protease inhibitors.

The first of these studies investigated the long-term antiviral activity and tolerability of Fortovase and nelfinavir in combination.[12] Fourteen HIV-infected persons with CD4 counts of 25–500 cells/mm³ and plasma HIV RNA levels >20 000 copies/ml were included in the study after completion of a formal

pharmacokinetic study (pharmacokinetic data are presented in chapter 2 (page 13)). Participants were treated with Fortovase 800 mg tid plus nelfinavir 750 mg tid, with the addition or continuation of up to two licensed RTIs. After 1 year of therapy, the median decrease in HIV RNA load was 2.4 $\log_{10}$ copies/ml and the median increase in CD4 count was 101 cells/mm³. Seven of the 9 persons remaining on study therapy at 1 year had an HIV RNA load of <500 copies/ml. The combination was well tolerated and no treatment-related serious adverse events or clinically significant laboratory abnormalities were noted.

Based on the promising findings from this pilot study, a second, phase II, open-label, randomised trial was conducted in 12 centres in Europe. SPICE (**S**tudy of **P**rotease **I**nhibitors in **C**ombination in **E**urope) compared the activity and safety of Fortovase plus nelfinavir with or without two RTIs with that of Fortovase plus two RTIs and nelfinavir plus two RTIs.[13] HIV-positive adults (≥13 years of age) with HIV RNA levels ≥10 000 copies/ml were enrolled if they had received ≤2 weeks of previous protease inhibitor therapy and were able to start therapy with two RTIs, one or both of which they were naïve to or had taken previously for ≤4 weeks. At least 50% of individuals enrolled were antiretroviral-naïve. Eligible persons were randomised in a 1:1:2:2 ratio to:
- Fortovase 1200 mg tid plus two RTIs
- nelfinavir 750 mg tid plus two RTIs
- Fortovase 800 mg tid plus nelfinavir 750 mg tid plus two RTIs
- Fortovase 800 mg tid plus nelfinavir 750 mg tid.

A total of 157 participants with mean baseline HIV RNA levels and CD4 count, respectively, of 4.8 $\log_{10}$ copies/ml and 301 cells/mm³ were enrolled. Subjects were allowed to cross over to another study arm in the case of toxicity or, after 16 weeks, virological failure or non-response.

After 32 weeks' therapy, plasma HIV RNA levels were below the 400 copies/ml detection limit of the Amplicor assay in 83% of those receiving Fortovase plus nelfinavir plus two RTIs, 70% receiving

Fortovase plus two RTIs, 69% receiving Fortovase plus nelfinavir without RTIs, and 55% receiving nelfinavir plus two RTIs. Furthermore, HIV RNA levels were 'undetectable' with the new UltraSensitive assay (<50 copies/ml) in 70% of persons in the quadruple-therapy arm, compared with 55%, 50% and 39% of those receiving Fortovase plus two RTIs, nelfinavir plus two RTIs and Fortovase plus nelfinavir without RTIs, respectively. However, a significant number of patients who did not achieve adequate viral load suppression on Fortovase plus nelfinavir without RTIs crossed over to the quadruple therapy arm. All study regimens were generally well tolerated, with the majority of adverse events being gastrointestinal.

These two studies demonstrate that the combination of Fortovase plus nelfinavir provides durable and potent suppression of HIV while retaining the good tolerability profiles of these two protease inhibitors. The addition of RTIs clearly enhances the activity of the combination and may be beneficial in certain individuals.

Combination with ritonavir

The combination of saquinavir plus ritonavir has been studied extensively using Invirase. The data show potent suppression of viraemia in the plasma and CSF out to 2 years.[16] There are no trial data at present pertaining to the antiviral activity of Fortovase in combination with ritonavir.

Summary

Clinical studies have shown Fortovase to be a highly active and well-tolerated antiretroviral agent. When given in combination with two RTIs, Fortovase produces prolonged and profound suppression of plasma viraemia, reducing plasma HIV RNA levels to below the quantification limits of currently available assays. The addition of a second protease inhibitor, such as nelfinavir, further augments this activity while still retaining a favourable tolerability profile. This approach may be of greatest value in individuals with high baseline HIV RNA load or extensive prior antiretroviral agent experience.

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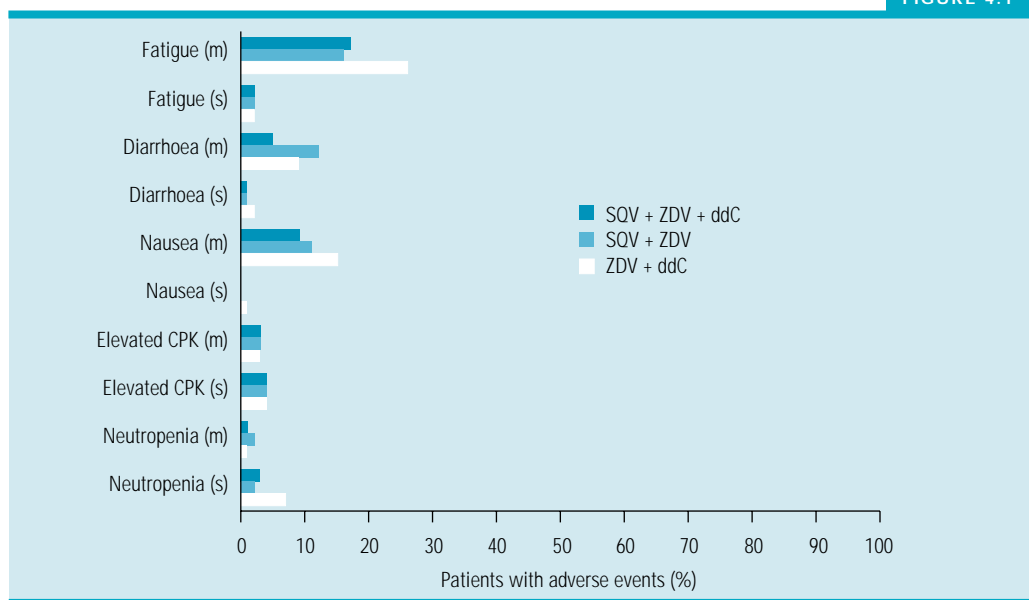
4 Fortovase: tolerability and safety

Extensive clinical experience with the hard gel formulation (>138 000 individuals treated) has shown saquinavir to be well tolerated in combination with a variety of nucleoside analogues.[1–5] In clinical studies of Invirase, most of the adverse events reported were deemed mild in intensity. The majority of adverse events were related to the gastrointestinal system and included diarrhoea, abdominal discomfort, vomiting and nausea (fig. 4.1). Unlike the nucleoside analogues, Invirase shows no evidence of dose-limiting toxicity, and it does not appear to alter the toxicity profile of these agents when used in combination with them.[1,2]

'Saquinavir has an excellent safety profile with few adverse events reported to date'.[2]

FIGURE 4.1

Proportion of 302 patients with moderate (m) or severe (s) adverse events during triple- and double-combination regimens with Invirase 600 mg tid, zidovudine 200 mg tid and ddC 0.75 mg tid in trial ACTG229.[4]

Legend:
- SQV + ZDV + ddC
- SQV + ZDV
- ZDV + ddC

Categories: Fatigue (m), Fatigue (s), Diarrhoea (m), Diarrhoea (s), Nausea (m), Nausea (s), Elevated CPK (m), Elevated CPK (s), Neutropenia (m), Neutropenia (s)

X-axis: Patients with adverse events (%) — 0 to 100

The most frequently reported adverse events were gastrointestinal

Experience with Fortovase

The safety profile of Fortovase has been extensively investigated in study NV15182, which analysed the safety and tolerability of Fortovase 1200 mg tid in combination with nucleoside analogues of choice, over a period of 48 weeks. There was no requirement to start a new RTI at initiation of study therapy, but concomitant medication could be changed at any time during the study.[6]

The study was performed in a broad study population (n=442), with no HIV RNA or CD4 entry criteria. Nor was there any restriction on the choice of concomitant RTIs. Approximately 95% of participants were receiving two RTIs, which included 3TC (73% of all patients), ZDV (65%), d4T (32%), ddC (12%) and ddI (12%). Participants had previously received HIV therapy for a mean of 4 years, and ≤25% were protease inhibitor-experienced. The long study

period and the size and heterogeneity of the study group render the results from this study a good model of the practical clinical situation.

Clinical adverse events are presented in table 4.1; as with Invirase, the most frequently reported events were gastrointestinal. There were only 6 serious

Adverse event	NV15182 (antiretroviral-pretreated)	NV15355 (antiretroviral-naïve)	
	Fortovase[b] + ToC (n=442)	Invirase[c] + two RTIs (n=81)	Fortovase[d] + two RTIs (n=90)
Gastrointestinal			
Diarrhoea	19.9	12.3	15.6
Nausea	10.6	13.6	17.8
Flatulence	8.6	4.9	13.3
Abdominal discomfort	8.4	–	8.9
Abdominal pain	5.7	7.4	12.2
Dyspepsia	2.9	1.2	4.4
Vomiting	2.3	1.2	7.8
Constipation	–	–	3.3
Whole body			
Fatigue	4.8	6.2	6.7
Nervous system			
Headaches	5.0	4.9	8.9
Psychiatric			
Depression	2.7	–	–
Insomnia	–	1.2	5.6
Anxiety	–	2.5	2.2
Libido disorder	–	–	2.2
Special senses			
Taste alteration	–	1.2	4.4
Musculoskeletal			
Musculoskeletal pain	–	3.7	3.3
Dermatological			
Eczema	–	2.5	–
Rash	–	2.5	–
Verruca	–	–	2.2

TABLE 4.1

Percentage of patients experiencing adverse events[a] in studies NV15182[6] and NV15355[7]

[a] Clinical adverse experiences, occurring in ≥2% of patients and considered at least possibly related to study drug or of unknown relationship but of moderate, severe or life-threatening intensity.
[b] 1200 mg tid for 48 weeks.
[c] 600 mg tid for 16 weeks.
[d] 1200 mg tid for 16 weeks.
Abbreviations: RTI = reverse transcriptase inhibitor; ToC = treatment of choice.

Fortovase is well tolerated by both antiretroviral-experienced and -naïve persons

adverse events that were considered at least possibly related to study therapy, of which 5 were gastrointestinal. No deaths related to the study drug occurred. While some marked biochemical abnormalities were noted, <1% of participants discontinued study therapy for this reason (table 4.2).

The safety and efficacy of both formulations of saquinavir have also been directly compared in study NV15355.[7] This multicentre, open-label study randomised antiretroviral-naïve persons to receive two nucleoside analogues of choice plus either Fortovase 1200 mg tid (n=90) or Invirase 600 mg tid (n=81) for 16 weeks.

Both regimens were generally well tolerated; although the Fortovase group experienced a slight increase in the frequency of gastrointestinal adverse events, most of these were mild in intensity (see table 4.1). Biochemical parameters are shown in table 4.2. There were no reports of deaths or serious adverse events related to treatment.

With the exception of an increase in the incidence of some gastrointestinal events, therefore, Fortovase has a side-effect profile similar to that of Invirase and is well tolerated by both antiretroviral-experienced and -naïve persons. As adherence to the drug regimen is now recognised as an important factor in determining ultimate effectiveness, the good tolerability and low incidence of serious side-effects reported is a significant clinical advantage of Fortovase therapy.

Percentage of patients with marked laboratory abnormalities (shifts of three ACTG grades) following triple therapy including Fortovase or Invirase in studies NV15182[6] and NV15355[7]

TABLE 4.2

Parameter	NV15182	NV15355	
	Fortovase[a] (n=442)	Invirase[b] (n=81)	Fortovase[c] (n=90)
↓ Glucose	6%	3%	4%
↑ CPK	8%	0%	5%
↑ GGT	6%	3%	7%
↑ ALT	6%	1%	2%
↑ AST	4%	0%	1%
↑ Potassium	3%	0%	1%
↑ Bilirubin	2%	0%	0%
↓ Neutrophils	3%	3%	1%
↓ Haemoglobin	1%	0%	1%

[a] 1200 mg tid for 48 weeks.
[b] 600 mg tid for 16 weeks.
[c] 1200 mg tid for 16 weeks.
Abbreviations and symbols: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatinine phosphokinase; GGT = γ-glutamyl transferase; ↑ = increase; ↓ = decrease.

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5 Reduced HIV sensitivity to saquinavir

In the absence of a known 'cure' for HIV, individuals infected with this virus are likely to be managed long term using combination regimens that are adjusted or sequenced in response to virological failure. There is mounting evidence to suggest a relationship between the emergence of drug-resistant HIV mutations and virological and clinical failure. Therefore, decisions regarding choice of treatment should not be made solely on the basis of anti-HIV activity or clinical efficacy of individual agents, but also with consideration of known resistance profiles. Indeed, there is the potential for some antiretroviral agents to compromise future use of others through generation of cross-resistant virus.

> **Choice of treatment should not be made solely on the basis of efficacy, but also with consideration of known resistance profiles**

The most common mechanism by which resistance develops is by a mutation affecting the site at which the drug binds to its target protein. This type of mutation is only beneficial to the virus if the normal function of the protein is not adversely affected. However, there may be a balance between the benefit gained from reduced drug sensitivity and the partial loss of viral replication efficiency.

Experience with Invirase

Resistance

> **Reduced sensitivity to Invirase is associated with two characteristic substitutions in the HIV protease gene: G48V and L90M**

Over 4000 full sequences of the HIV protease gene have been derived from patients prior to and during therapy with Invirase.[1] Analysis of these data confirm that reduced sensitivity to saquinavir is associated with two characteristic mutations of the protease gene, giving rise to:
- a glycine-to-valine substitution at position 48 (G48V)
- a leucine-to-methionine substitution at position 90 (L90M).[2]

Importantly, neither of these mutations was detected in HIV RNA from protease inhibitor-naïve persons (table 5.1),[2–7] indicating that they are debilitating to the virus. This may explain in part why reduced sensitivity to saquinavir develops at a low frequency. It also suggests that virus from individuals previously untreated with a protease inhibitor should be sensitive to saquinavir.[1]

In contrast, mutations at codons 46I and 82A, which have been associated with reduced sensitivity to indinavir, have been detected in a number of individuals at baseline. While the frequency of these substitutions at baseline is not very high, their detection indicates that there is a potential reservoir of resistant virus that may be selected for once indinavir is used.

In vivo, the L90M mutation predominates but has only a modest effect on HIV sensitivity to saquinavir. Indeed, sensitivity is usually reduced by less than 10-fold, with >40% of clinical isolates having less than a 4-fold reduction.[1] Although the G48V mutation has a greater impact on drug sensitivity, it occurs only rarely, which suggests that this is a particularly disadvantageous mutation. This has been supported by sequencing data from study NV14256, which compared Invirase, ddC and the two drugs in combination.[8] In plasma samples from a random selection of 60 HIV-infected individuals, the incidence of the L90M mutation after >40 weeks of treatment was

TABLE 5.1

Study	No. of patients	No. of sequences	Variant (%)									
			10V	36I	46I	48V	63P	71T/V	82A/I	84V	90M	93L
Jacobsen et al.[2]	24	313	2	–	0.3	0	34	0.3/0.3	0.3/5	0	0	–
Barrie et al.[3]	12	60	5	7	0	0	55	0/1.6	0/0	0	0	2
Kozal et al.[4]	102	167	0	4	3	0	51	1/0	0/3	0	0	20
Lech et al.[5]	12	246	0	11	0.4	0	>50	0/0	0/22	0	0	24
Schapiro et al.[6]	19	NA	–	–	–	0	–	–	–	–	0	–
Molla et al.[7]	42	NA	10*	12.5	0	–	60	–/2.5	0/0	0	0	19*
Barrie et al.[3]	NA	>250	–	–	0	0	+	+	–/0	0	0	+

Abbreviation and Symbols: NA = not available; + = detected; * = mutant amino acid not specified; – = not tested.

Incidence of HIV protease variants among clinical isolates from protease inhibitor-naïve subjects

41% in the Invirase monotherapy arm and 21% in the combination arm. The G48V mutation was only identified in 3 (5%) of the 60 samples.

Cross-resistance

Different protease inhibitors are associated with different mutation patterns, dependent on the precise orientation and interaction between drug and target. If the mutations are identical, resistance acquired through treatment with one drug may result in cross-resistance to another.

Saquinavir has a unique initial resistance profile. The first two mutations to appear during Invirase therapy, L90M and G48V, do not appear to induce significant cross-resistance, with the virus remaining susceptible to a range of other protease inhibitors.[9–11] However, continued administration of a protease inhibitor following loss of viral load suppression will increase the likelihood of acquiring multiple secondary mutations (fig. 5.1),[12] which may partially restore enzyme functionality. Data

suggest that residue changes to 10I, 63P/Q/T or 71T/V may be significant secondary substitutions.[13] Such mutations increase the risk of cross-resistance to other protease inhibitors, and therefore switching to another protease inhibitor at the first sign of virological failure should be advised. This should help ensure maximal benefit from the next regimen. In accordance with current guidelines, at least one of the RTIs should also be changed.[14,15]

In one study, following 1 year of Invirase therapy, 78% of persons treated were still fully sensitive to the drug and only 10% demonstrated cross-resistance to at least one other protease inhibitor.[16] These figures compare favourably with those reported by Condra et al., who found that 100% of individuals who had become resistant to indinavir during therapy with this agent were also cross-resistant to ritonavir.[17] It is notable that indinavir and ritonavir frequently induce mutual cross-resistance, as they both generate similar mutation patterns, particularly with substitutions at the protease residue 82.

The absence of G48V and L90M at baseline may explain why reduced sensitivity to saquinavir develops at a low frequency

Switching therapy at the first sign of virological failure should help ensure maximal benefit from the next regimen

FIGURE 5.1
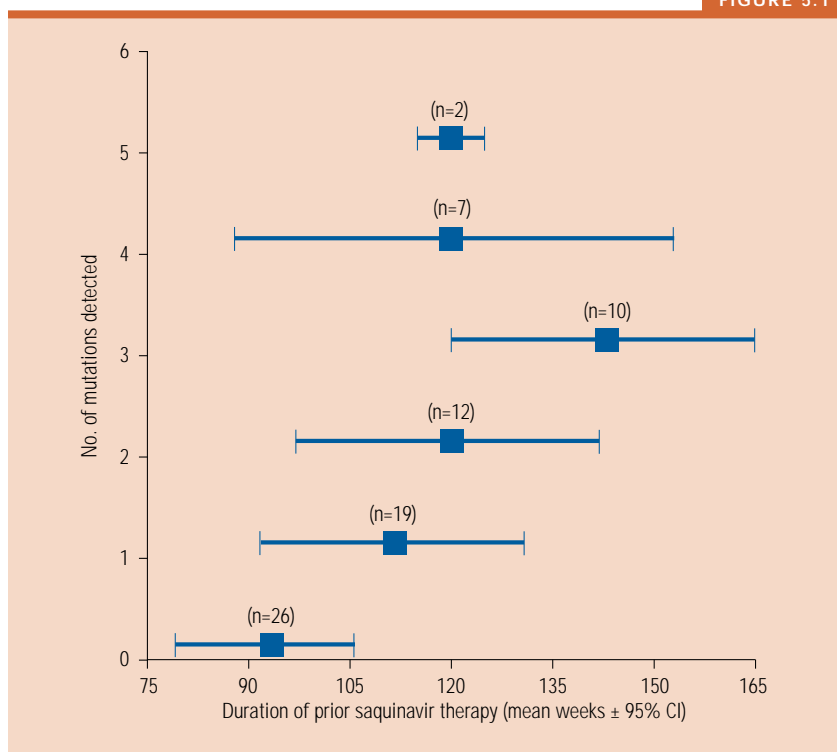
Number of HIV protease mutations detected with increasing pretreatment with saquinavir (Invirase). (Trial ACTG 333; reproduced with permission from the AIDS Clinical Trials Group).[12]

Clinical data on switching from one protease inhibitor to another

There are limited clinical data on switching from one protease inhibitor to another. These data suggest that the greatest benefit is attained in individuals who switch therapy in a timely fashion and change two or more antiretroviral drugs.

Study ACTG333 investigated switching HIV-infected persons from long-term treatment with Invirase to either Fortovase or indinavir. However, the nucleoside analogue components of the existing regimens were not changed. At baseline, median HIV RNA load was 4.3 $\log_{10}$ copies/ml and median CD4 count was 222 cells/mm^3. After a median of 112 weeks' therapy with Invirase, participants did demonstrate some benefit from switching to indinavir, experiencing a mean HIV RNA reduction of 0.58 $\log_{10}$ copies/ml after 8 weeks of therapy.[18] However, this modest reduction highlights the significant role of additional components of the combination regimens.

Although at the time that ACTG333 was initiated switching only one component of a failing regimen was accepted, current guidelines now recommend that changes in therapy should involve at least two agents.[14,15] The rationale for this is that after prolonged therapy, resistance may have developed to several of the components of the regimen. Thus by switching only one of the agents, the new regimen might essentially behave as monotherapy.

The benefit of changing more than one drug is confirmed in a retrospective analysis in which 33 patients who had received Invirase for a mean of 33 weeks either had ritonavir added into their regimen or were switched from Invirase to indinavir.[19] After 4–8 weeks, HIV RNA load had dropped by 1.72 and 1.57 $\log_{10}$ copies/ml in the ritonavir and indinavir arms, respectively. However, within each of the two groups, those individuals whose nucleoside analogues were also changed showed a greater response (table 5.2). Preliminary data indicate that these observations are supported to week 28 of the study.

Schapiro and colleagues reported similar results in a prospective study in individuals who received extensive pretreatment with high-dose saquinavir (3.6 or 7.2 g/day), predominantly as monotherapy.[10] Study participants were switched to indinavir for 1 month, after which they also received ZDV and 3TC. The mean HIV RNA level at baseline was 4.48 $\log_{10}$ copies/ml. Despite having received long-term Invirase (mean duration 58 weeks), in some cases accompanied by multiple mutations, an HIV RNA reduction of 1.9 $\log_{10}$ copies/ml was recorded after 24 weeks' therapy with the new regimen.

In one study of a cohort with advanced HIV infection, some of whom switched to indinavir-containing regimens after saquinavir therapy of variable duration, there was a modest trend favouring greater viral load response in those pretreated for less time (HIV RNA levels decreased by 1.2, 0.94 and 0.70 $\log_{10}$ copies/ml after 0, 0–4 and ≥4 months, respectively, of saquinavir pretreat-

Viral load was reduced by 1.9 $\log_{10}$ copies/ml after 24 weeks' therapy with indinavir plus ZDV plus 3TC in persons switching following long-term Invirase

TABLE 5.2

	HIV RNA reduction ($\log_{10}$ copies/ml)	
	Invirase + NAs + RTV	IDV + NAs
All patients	1.72 (n=19)	1.57 (n=14)
Only protease inhibitor therapy changed	1.61	1.38
Protease inhibitor and NA therapy changed	2.11	1.71
Abbreviations: IDV = indinavir; NA = nucleoside analogue; RTV = ritonavir.		

Change in viral load (HIV RNA) among patients changing from Invirase + NAs to Invirase + NAs + RTV or IDV + NAs (4- to 8-week analysis)[19]

ment).[20] This highlights the importance of a timely switch to a second regimen at the first appearance of virological failure.

Fortovase and increased exposure

Mutations that are observed *in vivo* occur as a result of selection pressure exerted by the drug. It was therefore theoretically possible that the greater saquinavir exposure attained with Fortovase would result in a change in either frequency or location of mutated residues. This issue is being addressed in a number of virological studies of persons who have received therapy with Fortovase.

Sequencing of the HIV protease gene was performed on plasma samples obtained from all 32 participants in the dose-ranging NV15107 trial who had received Fortovase 1200 mg tid for a median of 32 weeks. These data confirm that G48V and L90M are the key mutations arising with saquinavir therapy. However, in contrast to observations with the hard gel formulation, the two mutations were detected at approximately the same incidence, suggesting that the virus-debilitating G48V mutation may appear relatively more frequently with the new soft gel formulation.[21] This difference in incidence is yet to be confirmed in a Fortovase efficacy study.

In a study of 442 antiretroviral-experienced persons receiving Fortovase in combination with RTIs (study NV15182), 14 individuals (3%) who experienced viral relapse (defined as an increase in plasma HIV RNA of ≥1 $\log_{10}$ copies/ml) underwent protease genotyping after 16–24 weeks' therapy. Of

these, the 48V mutation was found in 2 persons, the 90M in 4, and both in 4. These results suggest that the 48V and 90M mutations remain closely associated with virological failure.

The genotypic resistance profiles of Invirase and Fortovase have been compared in a substudy of NV15355, which included antiretroviral-naïve persons with plasma HIV RNA levels >5000 copies/ml.[21] Individuals from both the Fortovase (n=28) and Invirase (n=26) arms were selected at random for genotyping. Protease genes were detected in both baseline and 16-week plasma samples in 10 and 17 participants, respectively. As a result of the efficacy of therapy with respect to inhibiting viral replication, there was a high proportion of individuals with insufficient virus for detection. In the Fortovase arm, few additional variants were observed compared with baseline. No G48V mutations were observed in either group, either at baseline or after 16 weeks' therapy. L90M was detected after therapy in only one person, who was receiving Fortovase. After 24 weeks' Fortovase therapy, only one further 48V substitution was detected.

These preliminary studies demonstrate a pattern of substitutions after Fortovase therapy consistent with that already reported with the hard gel formulation. They suggest that Fortovase does not give rise to increased early selection of key variants at positions 48 and 90, nor of variants associated with reduced sensitivity to other protease inhibitors. Although encouraging, longer-term studies are required to confirm these preliminary findings.

Preliminary studies demonstrate a pattern of substitutions after Fortovase therapy consistent with that already reported with Invirase

Summary

In summary, therapeutic strategies should acknowledge the likely development of drug-resistant mutants and plan for an eventual switch to different agents. Therapy should be initiated with a potent combination of drugs, including at least one protease inhibitor and two RTIs.[14,15] Therapy should be switched at the earliest sign of virological failure in order to minimise development of further multiple mutations, and the new regimen should include at least two new drugs. Initial loss of sensitivity to both the hard and soft gel formulations of saquinavir is associated with two key mutations (G48V and L90M). These occur slowly and by themselves do not appear to give rise to cross-resistance to other protease inhibitors. Their non-detection in baseline, wild-type clinical isolates indicates that these mutations are debilitating to the virus and suggest that persons naïve to protease inhibitor therapy should be sensitive to saquinavir. As the patterns of substitutions in the protease gene are similar for both formulations, individuals failing on Invirase as a result of selection of protease variants are unlikely to gain significant additional benefit from switching to Fortovase.

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6 Implications for patient management

Current trends in the management of HIV infection

In recent years, HIV therapy has shifted towards use of potent antiretroviral regimens earlier in the course of HIV infection. These changes have been driven by the availability of new antiretroviral agents coupled with a greater understanding of the pathogenesis and dynamics of HIV. It is now apparent that the primary damage inflicted by HIV is associated with active virus replication. Furthermore, there is now mounting evidence that HIV load (as measured by plasma HIV RNA levels) is an excellent predictor of disease progression.[1,2] Accordingly, the goals of antiretroviral therapy are now to improve survival and well-being through optimal and sustained viral suppression.

In view of these findings, updated guidelines from the International AIDS Society US panel and the US Health and Human Services recommend the use of triple-drug regimens comprising one protease inhibitor plus two RTIs for initial therapy in HIV-infected individuals.[3,4] The decision regarding which protease inhibitor to use, and when to use it, will depend upon a variety of factors, including:

- activity in different cell types, at different stages of infection
- tolerability and safety
- convenience of administration
- patterns of viral resistance and cross-resistance
- interactions with concomitant medications
- clinical history and current clinical status of the individual concerned.

Fortovase: the protease inhibitor of choice

Fortovase is licensed for use in combination with other antiretroviral agents for the treatment of HIV infection. This indication is based upon the established clinical benefits of the hard gelatin capsule formulation of saquinavir coupled with the impressive surrogate marker responses seen in the trials with Fortovase. Data from these studies indicate that Fortovase represents a logical choice for first-line therapy, combining potency and good tolerability in a convenient dosage regimen of 3-times-daily with food.[5]

Mode of action

- Fortovase acts at a late stage in the HIV replication cycle, making it effective in chronically infected cell lines.
- Fortovase acts at a stage of the replication cycle that is different from that with the RTIs, and this makes it a logical choice for combination with nucleoside analogues, resulting in dual sites of attack.
- Fortovase has a high degree of specificity for HIV protease, resulting in a very clean side-effect profile and thus a better chance of long-term tolerability.
- Fortovase does not require intracellular metabolic activation and is active in a wide range of cell types.

Resistance

- Strains of HIV that are less sensitive to the effects of Fortovase are slow to emerge and relatively infrequent. When they do occur, the loss of sensitivity associated with them is generally low.
- The mutations *initially* selected for by Fortovase are not seen in virus isolated from antiretroviral-naïve patients and are distinct from those selected for by other protease inhibitors. Fortovase is therefore an ideal protease inhibitor for first-line use.
- At the first sign of viral rebound, treatment should be switched to a different regimen comprising a new protease inhibitor and as many new components as possible; this should minimise the occurrence of resistant viral strains.
- The increased saquinavir exposure provided by Fortovase compared with Invirase does not appear to increase the frequency of protease gene mutations.

Pharmacokinetic properties

- At the recommended dosage (1200 mg tid), Fortovase achieves saquinavir plasma levels approximately 8-fold greater than those attained with the standard dosage of Invirase.
- Compared with other protease inhibitors, Fortovase has a relatively low potential for adverse drug interactions. Saquinavir has no appreciable metabolic interaction with ZDV or ddC.
- Fortovase is metabolised mainly by the CYP3A4 isozyme of cytochrome P450, and agents that induce this isozyme may reduce the plasma levels of saquinavir. Conversely, agents that inhibit this isozyme will increase saquinavir exposure.

Efficacy in combination therapy

- Large clinical-endpoint studies with Invirase have confirmed that incorporating saquinavir into combination regimens significantly delays progression to AIDS or death in both antiretroviral-naïve and -experienced HIV-infected persons.
- The significantly greater plasma exposure achieved with Fortovase compared with Invirase

has been shown to translate into more potent suppression of plasma viraemia. For example, in study NV15355, 80% of those in the Fortovase plus two RTIs arm had subquantifiable HIV RNA levels (<400 copies/ml) at week 16, compared with 43% in the Invirase plus two RTIs arm (p=0.001).[6]
- In antiretroviral-naïve and -experienced persons, Fortovase plus two RTIs was as effective as indinavir plus two RTIs in reducing viral load. In both treatment groups, plasma HIV RNA dropped to subquantifiable levels (<400 copies/ml) in *all* recipients at week 24.[7]

Tolerability

- Results to date indicate that Fortovase has a side-effect profile similar to that of Invirase and is well tolerated by both antiretroviral-experienced and -naïve persons.
- Most adverse events reported in clinical trials with Fortovase were mild and were associated with the gastrointestinal system.

The place of Fortovase in HIV therapy

Initial triple therapy

- In 5 studies of Fortovase combined with two RTIs in antiretroviral-naïve populations, HIV plasma viral loads decreased below the level of quantification (<400 copies/ml) in 75–93% of subjects (table 6.1).[6–10]
- Fortovase combined with RTIs is a preferred option for first-line therapy, according to current US guidelines on HIV therapy.[4]

Dual protease therapy

- The recent availability of the UltraSensitive HIV Monitor RNA assay has allowed the monitoring of viral loads to considerably lower thresholds than was previously possible. Data obtained using this assay indicate that it would be judicious to treat patients, particularly those with high baseline viral load or who have received prior RTI therapy, with a regimen of increased potency.

First-line therapy with Fortovase plus two nucleoside RTIs. Summary of five clinical studies showing the proportion of antiretroviral-naïve subjects with HIV RNA levels below quantification (<400 copies/ml) at the indicated time.

		TABLE 6.1
Study	**HIV RNA <400 copies/ml (% of patients)**	**Time of assessment (weeks)**
CHEESE[7]*	93	24
NV15355[6]	80	16
SPICE[8]*	75	16
SUN[9]	91	20
NV15182[10]*	75	24

* Data shown for the antiretroviral-naïve subgroup of the study population.

- Early results suggest that the combination of Fortovase plus a second protease inhibitor with RTIs may offer the potency premium required in these patients. The combination of Fortovase plus nelfinavir plus two RTIs was shown to provide more profound suppression of plasma viraemia than triple therapy with two RTIs plus either of these protease inhibitors.[11] Similar results were obtained when Fortovase was combined with the new protease inhibitor amprenavir (VX-478; 141W94).[12]

Recipients of extensive prior antiretroviral therapy

- The combination of Invirase plus ritonavir has shown potent antiretroviral activity and is a recommended combination in this group.[4]

Dosage and administration
- Fortovase is supplied as soft gelatin capsules, which are tapered and lightly coated with oil for ease of swallowing. They should be taken whole.
- In combination with nucleoside analogues, Fortovase is dosed at 1200 mg three times daily. Reductions in dose will lead to greater than proportional reductions in plasma levels.
- In combination with other protease inhibitors, a reduction in Fortovase dose may be required (see page 22).

- Fortovase should be administered with or within two hours after a meal. As well as improving absorption, this aids regimen compliance.
- Unlike other PIs, which require complicated and strictly observed regimens including scheduled times for eating, drinking and taking medication, the regimen for Fortovase (and for nelfinavir) plus two nucleoside RTIs is conveniently structured three times daily, with meals serving as a reminder.

Summary
Clinical studies have confirmed that the greater plasma saquinavir levels achieved with Fortovase compared with those attained with Invirase result in a significant enhancement of its activity against HIV. Results to date indicate that Fortovase given in combination with two RTIs is an effective and well-tolerated treatment for HIV infection.

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Considerations when initiating Fortovase therapy

It has been shown that Fortovase provides a plasma exposure of saquinavir that is considerably greater than that achieved with Invirase. Clinical data show that the increased plasma exposure translates into significantly greater suppression of viral replication. Therefore, when initiating saquinavir therapy, Fortovase is recommended rather than Invirase.

Transferring from Invirase to Fortovase
- With the availability of Fortovase, there is no necessity for any individuals to continue receiving Invirase. However, those receiving Invirase in combination with ritonavir may not gain any additional advantage from a transfer to Fortovase. This is because of the increased plasma levels of saquinavir obtained when Invirase is coadministered with ritonavir.
- Other Invirase recipients who have HIV RNA levels below quantification may consider a switch to Fortovase.
- Individuals taking Invirase who have not had an adequate response or are failing therapy are not advised to switch to Fortovase.
- It should be noted that there is little past experience of individuals changing *formulation* of protease inhibitor (rather than the protease inhibitor *per se*), so these suggestions should be considered along with individual patient experience and viral load, and in agreement with the current guidelines on HIV therapy.

Fortovase® monograph

ROC7-571