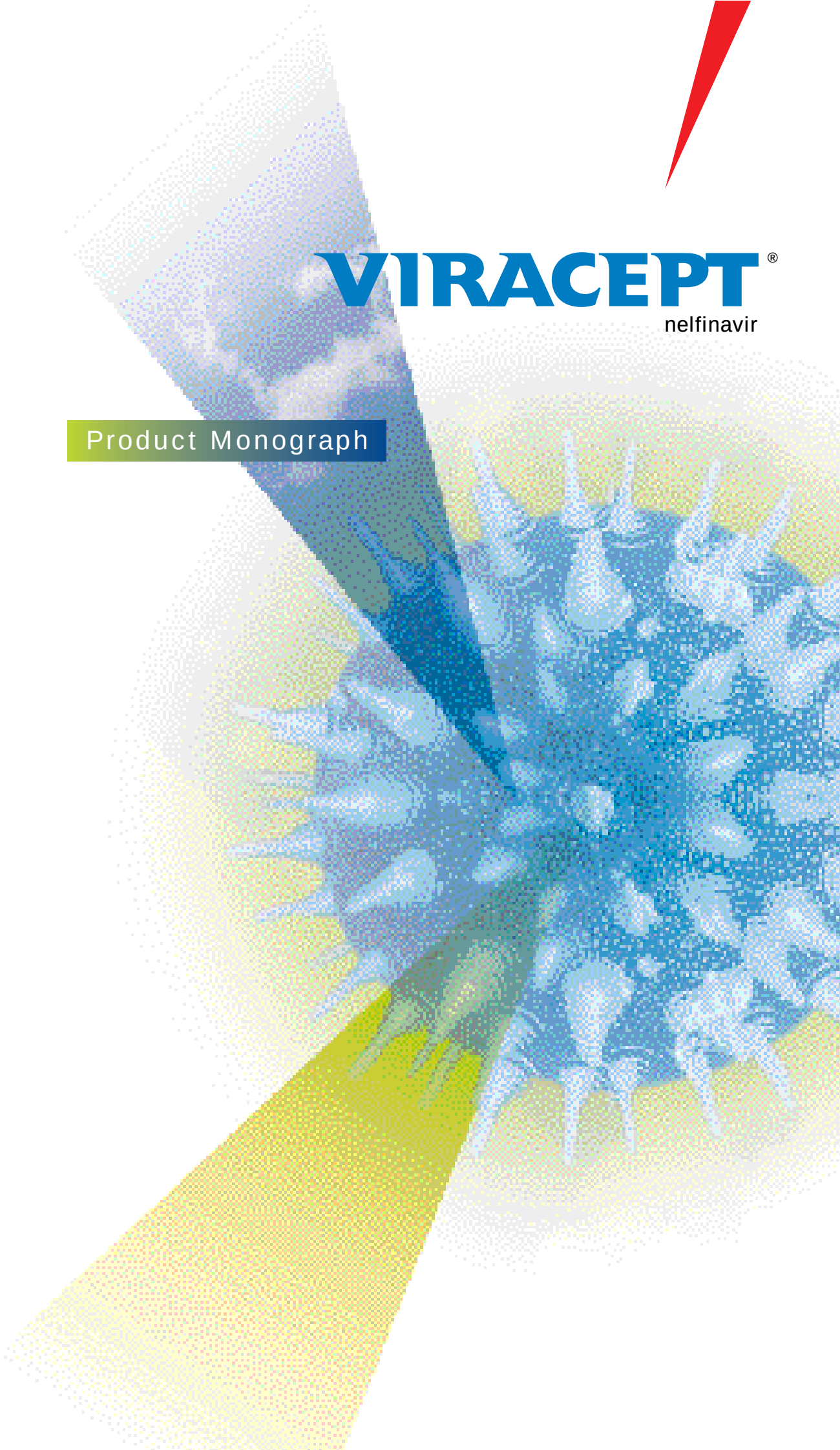
VIRACEPT®

nelfinavir

Product Monograph



Contents

1 Introduction

Viracept (nelfinavir mesylate) is a novel protease inhibitor indicated for use in combination with reverse transcriptase inhibitors for the control and management of HIV infection. Viracept is a potent inhibitor of viral replication. When used in combination with nucleoside analogues, Viracept is a highly effective protease inhibitor, reducing viral load and increasing CD4 levels, thus meeting the criteria required of an effective antiretroviral agent. Antiviral resistance to Viracept does not appear to develop rapidly, and in vitro results suggest that this protease inhibitor does not seem to confer or induce cross-resistance to other protease inhibitors. This introductory chapter sets the scene for a monograph in which Viracept is defined as the protease inhibitor that has the characteristics of an ideal first-line therapy for use in combination in the management of HIV disease.

Protease inhibitors offer a new opportunity in the treatment of HIV disease

Viracept is the most advanced of the available protease inhibitors, combining efficacy with good tolerability

Human immunodeficiency virus (HIV) infection continues to pose new and complex challenges to the medical community. Although the battle against infection has yet to be won, dramatic advances have been made in understanding the basic science of HIV. After years of endeavour, treatment options have now broadened, bringing greater promise of suppression and control of infection. Patients with HIV disease can now expect improved life-expectancy and a better quality of life than ever before.

Among the new and emerging antiretroviral therapies that have been pivotal in changing clinical practice are the protease inhibitors. This class of antiretroviral agent targets a step in viral replication distinct from that inhibited by the reverse transcriptase inhibitors. When used in combination with reverse transcriptase inhibitors, the protease inhibitors allow a two-pronged attack on viral replication, suppressing plasma HIV-RNA to below detectable levels of the most sensitive assays available (ultrasensitive if possible) in most treatment-naive patients. There are now at least five different protease inhibitors, licensed or in development, the most recently licensed of which – Viracept (nelfinavir mesylate) – is the topic of this monograph.

Current therapy guidelines

Management of HIV disease has changed radically in recent years, not only because of the availability of new and powerful antiretroviral agents, but also because insights into the pathology of infection have led to the widely accepted conclusion that the best strategy to control HIV infection is to hit the virus early and hard. The key goal in management is to suppress viral replication to undetectable levels. In this way, interventions and management strategies seek to prolong the asymptomatic phase of infection, to avoid irreversible destruction of the immune system, to prevent opportunistic infections, and so extend survival and improve quality of life for infected patients.

Guidelines on the management of HIV infection have been published by international panels of experts.[1–3] Recent guidelines from the US National Institutes of Health (NIH) recommend the use of three antiretroviral agents (one protease inhibitor and two nucleoside analogues) as the preferred combination for initiating anti-HIV treatment.

These recommendations were made on the grounds of strong clinical evidence and/or sustained suppression of plasma viral load.[4]

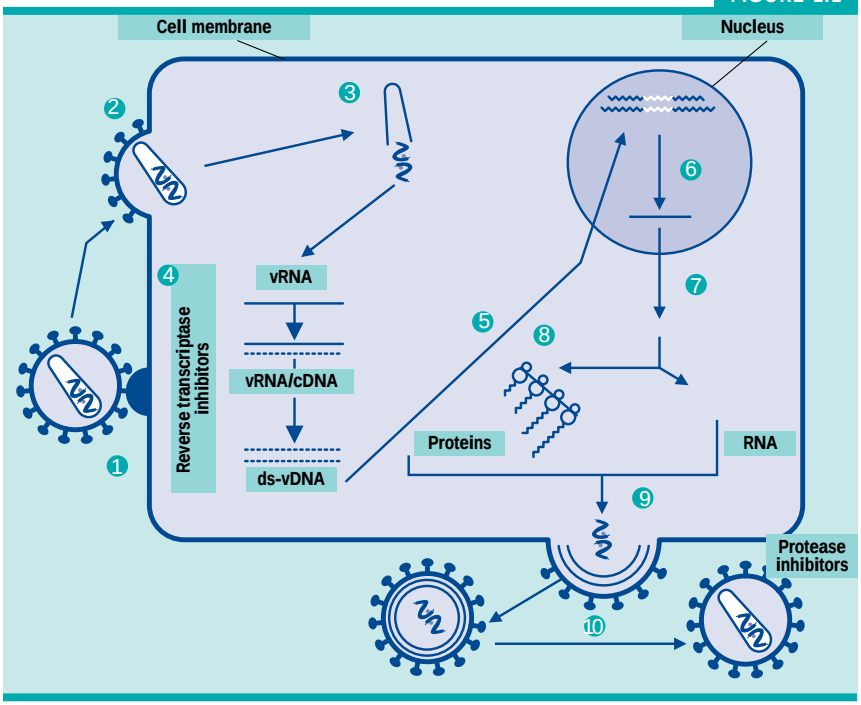
The guidelines highlight the importance of monitoring viral load in addition to assessing the traditional surrogate marker of HIV disease status – the $CD4^+$ lymphocyte count. It is now clear that plasma viral RNA ('viral load') is an independent predictor in assessing progression, with practical implications in determining status of infection. Various studies have demonstrated conclusively that plasma HIV-RNA levels are the most accurate predictor of clinical outcome for patients.[5–8]

It is recommended that optimal treatment for HIV infection constitutes a combination of agents that reduce plasma viral load to below the level of detection. Currently used assay systems have a cut-off sensitivity of 200–500 copies of HIV-RNA/mL; (Roche Amplicor® system or bDNA assay). Novel assays (i.e. Roche ultrasensitive assay) have detection limits as low as 20 copies/mL. Reducing plasma viral load to below detectable levels of the most sensitive assays available (ultrasensitive if possible) is very important, because partial suppression of viral replication allows more rapid selection of resistant variants, which ultimately can lead to treatment failure.

Life cycle of HIV – targets for antiretroviral therapy

1 *Attachment*
2 *Penetration*
3 *Uncoating*
4 *Reverse transcription*
5 *Integration*
6 *Transcription*
7 *RNA processing*
8 *Translation*
9 *Assembly*
10 *Maturation*

FIGURE 1.1



Combination antiretroviral therapy – the contemporary concept

Antiretroviral therapy seeks to attack HIV and suppress its replication. In theory, there are a number of targets for antiretroviral action (Figure 1.1), but in practice, only two of these targets in the HIV replication cycle have been exploited successfully. Agents that affect step two – inhibition of reverse transcriptase (by nucleoside analogues or non-nucleoside compounds) – and step six – inhibition of protein processing (by HIV protease inhibitors) – have been approved as therapies for the management of HIV disease.

Commonly used combination therapy employs three of the available antiretroviral agents – one of which is a protease inhibitor – to bring about maximal suppression of HIV replication over a prolonged period. Marked suppression of viral replication leads to improved clinical outcome, and appears to reduce the likelihood of drug resistance emerging.

The results of three major clinical studies have clearly demonstrated that the combination of two nucleoside analogues is superior to one nucleoside analogue.[9–11] Patients who received combined therapy experienced a significant delay in progression to AIDS or death, compared with those receiving nucleoside monotherapy.

More recently, three-drug combinations, involving two nucleoside analogues plus a protease inhibitor, have been shown to be yet more effective than two-agent combinations. For example, in a study comparing the protease inhibitor saquinavir plus zidovudine (AZT) plus zalcitabine versus zidovudine plus zalcitabine versus saquinavir plus zidovudine, significantly fewer clinical endpoints (i.e. a first AIDS-defining event or death) were noted in the triple combination group, compared with the other treatment

TABLE 1.1

Principles guiding drug choice in therapy combinations
Established activity and tolerability
History of prior drug exposure and source of HIV infection
History of medical conditions
Convenience of administration and formulation
Concomitant medications
Synergistic or additive activity in vitro of drugs used in combination
No, or low, potential for additive or synergistic toxicities of drugs used in combination regimens
No negative metabolic or intracellular pharmacokinetic interactions
Favourable resistance pattern
Activity in different cell lineages
CNS penetration

groups.[12] Similar results in favour of a three-drug combination were obtained in study ACTG 320,[13] which investigated a combination of two nucleoside analogues plus the protease inhibitor indinavir.

The right selection

Clinical data in this monograph show Viracept to be a potent protease inhibitor that is highly efficacious when used in combination with nucleoside analogues, readily producing the required degree of viral suppression and thereby preventing disease progression in patients with HIV disease. Used in combination with two nucleoside analogues, Viracept fulfils the requirement of an ideal antiretroviral agent, by hitting viral replication hard. These effects can be shown to be sustainable and linked to improvements in $CD4^+$ cell count. In addition to considering the efficacy of antiretroviral agents, the choice of agents used in combination (Table 1.1) is important in reducing the potential for HIV to develop drug resistance. This theme will be explored in greater detail in Chapter 5, where evidence is presented showing that the potent antiretroviral effects of Viracept afford this drug a low potential for the development of HIV resistance.

A key role for protease inhibitors

Protease inhibitors play a key role in contemporary HIV management. Although existing drugs in this class have been shown to be effective in suppressing viral load when used in combination with nucleoside analogues, there is a need for a potent protease inhibitor with improved tolerability and more convenient dosing that is less likely to promote the development of resistance. The profile and characteristics of Viracept appear to favour its use as a first-line protease inhibitor.

Saquinavir – the first protease inhibitor to be licensed for use in HIV disease (December 1995) – is a potent inhibitor of HIV protease (IC_{50}, 1–30 nM)[14] and has been studied extensively in patients at various stages of HIV disease. The other licensed protease inhibitors – indinavir and ritonavir – have inhibitory activity *in vitro,* and *in vivo,* but are associated with a higher incidence of side-effects than saquinavir.[15] Indinavir is also considered to have less convenient dosing schedules than Viracept, which is associated with only minor side-effects and has a convenient three-times-daily-with-food regimen.

Viracept – a distinct protease inhibitor

There is a clear need for a new antiretroviral agent with potent inhibitory activity and a good safety and tolerability profile, that is easy to administer and has a low potential for resistance when used in combi-

Combination therapy involving nucleoside analogues and Viracept leads to effective suppression of virus replication achieving reductions in plasma HIV-RNA below the level of detection

Viracept is an ideal protease inhibitor for use in first-line therapy

Viracept offers high potency combined with low toxicity and convenience of use

Viracept has undergone rigorous assessment and is poised to find a key position in the HIV armamentarium

Recent guidelines have selected Viracept as one of the preferred protease inhibitors to be used in initial antiretroviral combination regimens[4]

nation with reverse transcriptase inhibitors. These criteria are largely met by Viracept, a rationally designed compound that has been studied extensively, initially as monotherapy in phase I and II studies, and more recently in combination with one and with two nucleoside analogues.

Viracept has potent inhibitory activity on HIV protease and has been shown to decrease viral load significantly and increase $CD4^+$ cell counts when given as monotherapy. Even more pronounced improvements in these parameters are seen when Viracept is used together with nucleoside analogue antiretroviral therapies. A triple-agent regimen involving Viracept has been shown to suppress plasma HIV-RNA levels to below detectable levels in 80–85% of patients over 12 months.[16]

Viracept is well tolerated and easily administered; a powder formulation suitable for administration to children or patients unable to take tablets has also been developed recently.

Viracept offers high potency combined with low toxicity and is therefore poised to become the agent of choice among protease inhibitors. The following chapters examine the rigorous preclinical and clinical assessment of this new agent and help define a new product that will take its place in the first-line armamentarium of HIV therapies.

Recent guidelines issued by the NIH in the USA indicate that Viracept is one of the preferred protease inhibitors to be used in combination with two nucleoside analogues in patients beginning antiretroviral treatment.[4]

Summary

Viracept (nelfinavir mesylate) is a novel and potent protease inhibitor. In clinical studies, Viracept has been shown to be highly effective in combination with nucleoside analogues. The efficacy, safety and tolerability profile of Viracept suggests that it is well suited for use in first-line combination regimens in HIV disease management.

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2 Viracept – design and key product characteristics

Viracept is a product of rational drug design and is a potent inhibitor at the active site of HIV protease

Inhibition of HIV protease causes suppression of viral replication in acute and chronically infected cells

Viracept (nelfinavir mesylate) has demonstrated potent in vitro antiretroviral activity against many strains of HIV

Viracept (nelfinavir mesylate) is a potent inhibitor of HIV protease, a key enzyme in the maturation of infectious HIV. This compound was rationally designed from a detailed knowledge of the three-dimensional structure of the active site of HIV protease. In vitro studies have demonstrated that the inhibitory activity translates into potent antiviral activity. Viracept represents the latest and most advanced HIV protease inhibitor, combining high potency with a good safety profile unrivalled in its class.

Mechanism of action

HIV protease was first recognised as a potential target for antiretroviral therapy in 1986.[1] The quest to exploit HIV protease led to the development and licensing for clinical use of saquinavir (Invirase), and more recently to the development of newer protease inhibitors, of which Viracept is the most advanced.[2]

Prior to the development of protease inhibitors, all antiretroviral therapies (nucleoside analogues) targeted HIV reverse transcriptase. This enzyme is unique to the HIV virus and is essential to the conversion of the viral RNA genome into a double-stranded form that is integrated into the host genome. This step occurs early in the course of infection. Thus, nucleoside analogues are ineffective in chronically infected cells.

HIV protease is essential to the maturation of HIV particles, one of the final processes in the replicative cycle. The protease cleaves the gag-pol polyprotein into two separate functional proteins that are essential for the infectivity of the new virion. If the protease is inhibited, HIV particles still bud from the infected cell but are not infectious. Protease inhibitors thus act at a distinct step in the replicative cycle and are active in chronically infected cells as well as in acute infection.

Rational design and antiviral activity

Viracept was rationally designed using detailed knowledge of the three-dimensional structure of the active site of HIV protease. Repeated co-crystalisation of the enzyme with possible inhibitory compounds allowed optimisation of the ligand–enzyme interaction. Using this process, a number of novel compounds were identified, the most promising of which was nelfinavir mesylate (Viracept), which was found to have potent antiviral activity in *in vitro* models of acute and chronic infection (Table 2.1).[3]

Nelfinavir mesylate (Viracept) is a potent inhibitor of HIV protease. In *in vitro* model systems of HIV infection, nelfinavir has an EC_{95} (95% effective concentration) of between 7 and 111 nM (mean 58 nM)[4] (Table 2.1). Nelfinavir has demonstrated potent antiretroviral activity against a broad range of laboratory and clinical isolates of HIV-1 and the HIV-2 strain ROD, and is effective against chronic as well as acute infection. Results from *in vitro* studies of nelfinavir in combination with one and with two nucleoside analogues indicated that nelfinavir inhibits viral replication in a manner that acts synergistically with zidovudine, lamivudine and zalcitabine. Interactions with ddI or stavudine are at least additive.

TABLE 2.1

Key features of nelfinavir from in vitro *studies*

Potent antiviral activity: EC95 against in vitro viral replication, 7–111 nM (mean 58 nM)
Low cytotoxicity: TD50, 23–28 µM
Efficacy against a broad range of laboratory strains and clinical isolates of HIV-1 and HIV-2 strain ROD
Synergistic or additive interactions with nucleoside analogues in vitro • plus zidovudine, zalcitabine and/or lamivudine = synergistic • plus ddI and/or stavudine = additive

Viracept shows in vitro synergy with most nucleoside analogues

Clinical data presented in the next chapter provide evidence to support these early predictions that Viracept is a unique and promising protease inhibitor.

Summary

Viracept was designed to be a potent inhibitor of HIV protease. Results of in vitro studies show that Viracept has marked antiretroviral activity. The effects of Viracept are additive or synergistic with those of nucleoside analogues.

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3 Clinical experience

Clinical studies with Viracept have used measures of viral load (plasma HIV-RNA) and of $CD4^+$ cell count to assess the efficacy of therapy

Throughout extensive clinical trials, Viracept (nelfinavir mesylate) has been found to have potent antiviral activity, causing significant suppression of viral replication and improving $CD4^+$ cell counts in HIV-infected patients. A dose regimen of 750 mg t.i.d. taken with food provides maximal antiviral activity together with good patient tolerability, and is recommended for use in combination regimens with reverse transcriptase inhibitors (nucleoside analogues). The addition of Viracept to nucleoside combination therapy reduces viral replication such that the levels of plasma HIV-RNA fall below the limits of assay detection (i.e. plasma HIV-RNA < 400–500 copies/ml), thus achieving the goals set in recent guidelines for the management of HIV disease. This chapter provides clinical evidence supporting the use of Viracept as a first-line protease inhibitor.

Introduction

Viracept has been evaluated extensively in phase II and III clinical studies conducted in patients at different stages of HIV disease. Viracept was initially investigated as monotherapy and later in combination with one and two reverse transcriptase inhibitors (nucleoside analogues). The design and regimens of the main studies are summarized in Table 3.1.

In all studies, the efficacy of Viracept has been assessed by determining the effect of therapy on two widely accepted and validated indicators of disease status and progression: viral load (i.e. plasma HIV-RNA) and $CD4^+$ cell count. The plasma HIV-RNA level, or viral load, was assayed by measuring the number of copies of HIV-RNA per ml of plasma, with levels less than 400–500/ml being below the limits of detection using the standard assays available at the time of study.

It is now widely accepted that these two surrogate markers allow an accurate assessment of the level of HIV replication and the extent of destruction of the immune system, respectively. Clinical studies have validated the use of plasma HIV-RNA levels (viral load) and $CD4^+$ cell counts as reliable endpoints that are now routinely used to assess new therapies and novel combined treatment regimens.[1–17]

For example, the ACTG 175 trial validated the use of viral load as an acceptable marker and showed that the level of HIV-RNA in the plasma is a strong predictor of the relative risk of disease progression and time to death. This study, which involved 2400 HIV-positive patients, showed that reductions in HIV-RNA levels predicted for improved survival, and indeed, antiretroviral therapy both delayed disease progression and reduced mortality.[12]

More recently, it was shown that combination therapy involving protease inhibitors and nucleoside analogues is superior to the use of combined nucleoside analogue therapy – both in terms of effects on viral load and $CD4^+$ cell counts, as well as in terms of clinical outcome. Pivotal clinical studies with protease inhibitors, such as saquinavir (SV14604 and NV14256),[18,19] ritonavir[20] and indinavir (ACTG320),[21] which were planned to assess the effects of treatment on clinical endpoints, noted improvements in $CD4^+$ cell counts and reductions

TABLE 3.1

Summary of the design and regimens employed in phase II and III clinical studies of Viracept

Study number	Patient characteristics	Regimen	
		Viracept	Nucleoside analogue(s)
Phase II studies			
AG1343-510	39 patients; CD4 ≥ 200; HIV-RNA ≥ 15,000/ml; not previously received stavudine; 50% pts received ≥ 1 year antiretroviral therapy	500 mg t.i.d. + 750 mg t.i.d. + 1000 mg t.i.d. + placebo +	stavudine stavudine stavudine stavudine
AG1343-509	12 patients; mean CD4 = 258/mm^3; HIV-RNA ≥ 10,000; no prior antiretroviral therapy	750 mg t.i.d. +	zidovudine, 200 mg t.i.d., + lamivudine, 150 mg b.i.d.
Phase II/III studies			
AG1343-505	93 patients; CD4 ≥ 50; HIV-RNA ≥ 15,000/ml; 20% no prior antiretroviral therapy	500 mg t.i.d. 750 mg t.i.d. placebo (included in stage I of study but not stage II)	– – –
AG1343-506	306 patients; CD4 ≥ 50; HIV-RNA ≥ 15,000/ml	500 mg t.i.d. + 750 mg t.i.d. + placebo +	stavudine stavudine stavudine
AG1343-511	297 patients; HIV-RNA ≥ 15,000/ml	500 mg t.i.d. + 750 mg t.i.d. + placebo +	zidovudine + lamivudine

Reductions in viral load and increases in CD4$^+$ cell count are associated with delayed disease progression, improved survival and reduced mortality

in viral load that were found to correlate with improved clinical outcome.[22]

The Viracept clinical studies described here were all devised and planned to assess the effects of therapy on the proven, reliable measures of effect on viral load and CD4$^+$ cell count, so making it possible to accelerate the clinical development of this important new protease inhibitor.

Phase I studies

Two phase I studies were performed in normal individuals to determine the safety and tolerability of Viracept and to establish suitable doses for use in clinical studies.

In one of these studies – AG1343-501 – single doses (100, 200, 400 and 800 mg) were administered to 12 healthy volunteers. All doses resulted in plasma levels of nelfinavir that exceeded the ED_{95} value of 40 ng/ml required to suppress viral replication in laboratory studies. Viracept was well tolerated at all doses.

In a second phase I study – AG1343-502 – two doses (400 mg b.i.d. and 300 mg t.i.d.) were administered with food (known to improve the oral bioavailability of Viracept; see also Chapter 6) to 14 healthy volunteers for 7 days. Both of the regimens selected maintained steady-state trough levels above the ED^{95}.

Phase II monotherapy pilot studies

Two pilot dose-escalation studies (AG1343-503 and AG1343-504) were performed in HIV-positive patients to determine the most appropriate dose and schedule of administration for evaluation in the pivotal phase II/III studies. Study AG1343-503 was later extended to investigate two higher dose

TABLE 3.2

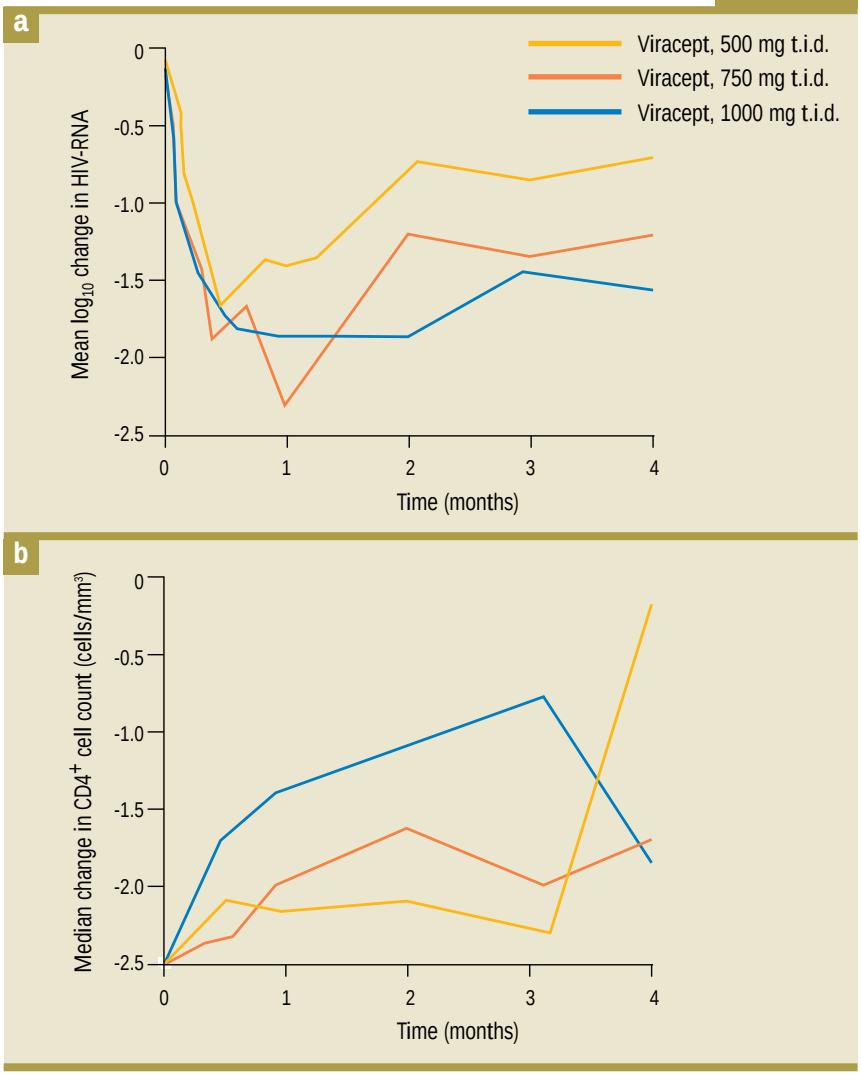
Summary of regimens and patient characteristics for the phase II monotherapy studies AG1343-503, AG1343-503B and AG1343-504.

Study	Patient characteristics	Viracept regimens
AG1343-503	65 patients CD4 ≥ 200 cells HIV-RNA ≥ 20,000 copies/ml	500 mg b.i.d. (1000 mg/day) 600 mg b.i.d. (1200 mg/day) 750 mg b.i.d. (1500 mg/day)
AG1343-503B	30 patients CD4 ≥ 200 HIV-RNA ≥ 20,000 copies/ml	500 mg t.i.d. (1500 mg/day) (group A) 750 mg t.i.d. (2250 mg/day) (group B) 1000 mg t.i.d. (3000 mg/day) (group C)
AG1343-504	22 patients CD4 200–500 cells HIV-RNA ≥ 20, 000 copies/ml	300 mg t.i.d. 400 mg t.i.d. 600 mg t.i.d.

(source AMA vol8 p39, IB p6-4)

FIGURE 3.1

(a) Mean change in HIV-RNA and (b) median change in absolute CD4$^+$ cell count during Viracept monotherapy in study AG1343-503B (n = 30)



regimens (study AG1343-503B). The treatment period for both studies was 28 days initially; other study details regarding patients and dosages are provided in Table 3.2.[23]

Study AG1343-504 showed suppression of viral load and improvement in CD4$^+$ cell count induced by Viracept. These responses to Viracept were demonstrated further in study AG1343-503 (and 503B), in which a dose–response effect on these two parameters was observed. The proportion of patients in whom virus levels fell to below the level of assay detection (i.e. HIV-RNA < 500/ml) was greatest in those receiving doses of 2250 mg/day or more.[24]

In study AG1343-503B, all doses of Viracept decreased HIV-RNA levels from their initial baseline values (Figure 3.1a). In addition, the increase in CD4$^+$ cell count from baseline was significant for all three doses, with a median increase in CD4$^+$ cell count of over 50 cells/mm^3 for the groups receiving Viracept, 750 mg t.i.d. and 1000 mg t.i.d. (Figure 3.1b). Extension of Viracept treatment for a further 3 months led to stabilization of plasma HIV-RNA to levels below baseline (mean log10 falls in viral load from baseline: Viracept, 500 mg t.i.d. = 0.6; Viracept, 750 mg t.i.d. = 1.2; Viracept, 1000 mg t.i.d. = 1.5), and a median increase in CD4$^+$ cell count of more than 50 cells/mm3 for all three doses.[23]
In these dose-finding studies, Viracept was gener-

ally well tolerated. Approximately 50% of patients reported diarrhoea of grade 2 or greater when receiving the 1000 mg t.i.d. regimen, compared with just 10% of patients receiving lower doses. These studies indicated that Viracept, 750 mg t.i.d., offers the best combination of efficacy and tolerability.[23,24]

Comparison with other protease inhibitors

The effects of Viracept on HIV-RNA levels and $CD4^+$ cell counts observed in these pilot studies (AG1343-503A, 503B and 504) are comparable to those seen in similar studies using other protease inhibitors.[24]

Phase II combination studies

During phase II investigations, Viracept was studied in combination with stavudine (study AG1343-510), and in combination with zidovudine plus lamivudine (study AG1343-509).

Study AG1343-510

Study AG1343-510 compared a combination of Viracept plus stavudine *versus* stavudine alone in a group of 39 HIV-positive stavudine-naive patients. The study was initially conducted over a 60-day period. At the start of the study, patients had plasma HIV-RNA titres of ≥ 15,000 copies/ml, and $CD4^+$ cell counts of ≥ 200 cells/mm^3. After a 2-week wash-out period (around half of all patients had been receiving antiretroviral therapy), patients were randomized to one of four treatment arms:[25]

- Viracept, 500 mg t.i.d., *plus* standard dose stavudine
- Viracept, 750 mg t.i.d., *plus* standard dose stavudine
- Viracept, 1000 mg t.i.d., *plus* standard dose stavudine
- standard dose stavudine (patients < 60 kg, 30 mg b.i.d.; > 60 kg, 40 mg b.i.d.).

Viracept combination therapy was associated with a more sustained suppression of viral load and a greater increase in $CD4^+$ cell count than was achieved with stavudine therapy alone. A dose–response relationship was observed, such that viral RNA titres (log_{10} decreases in HIV-RNA) were reduced by 1.7, 2.2 and 2.4 (log_{10}) for Viracept, 500 mg, 750 mg and 1000 mg regimens, respectively, compared with only a decrease of 0.8 for stavudine monotherapy. Thus, over the study period, patients who had received Viracept showed a cumulative reduction in viral load, compared with those receiving stavudine monotherapy ($p = 0.0008$) (as assessed by mean area under the curve AUCMB [log_{10}] values for plasma HIV-RNA). All three Viracept combination treatments led to an increase in $CD4^+$ cell count of over 100 cells/mm^3, compared with a median increase of 88 cells/mm^3 for stavudine therapy alone.[26,27]

After the initial 60-day evaluation period, the study was extended for a further 3 months. Patients who were previously given stavudine monotherapy were switched to the more effective combined regimen and randomized to one of the three Viracept groups. For the patients switching, the change in regimen led to an immediate decrease in viral load, and, by the end of 3 months of combination therapy, to a mean increase in $CD4^+$ cell count of 175 cells/mm^3 above baseline (Figure 3.2).[28,29]

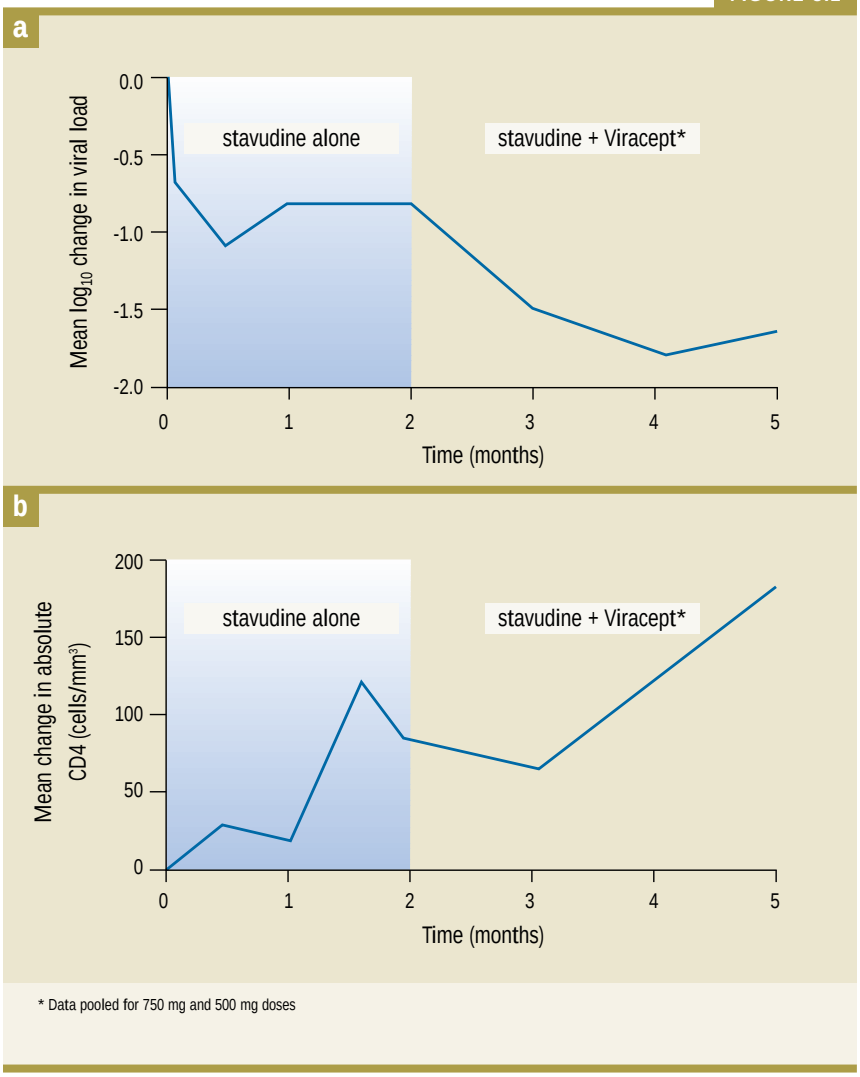
Thus, after a total of 5 months of therapy (60 days initial assessment and 3 months extension), HIV-RNA levels stabilized at mean log_{10} decreases of 1.3 (Viracept, 500 mg t.i.d.), 1.7 (Viracept, 750 mg t.i.d.) and 1.8 (Viracept, 1000 mg t.i.d.) below baseline. After 4 months of therapy, a median increase of 150 $CD4^+$ cells/mm^3 was seen for the three different Viracept doses.[26]

During the course of this study, which clearly demonstrated the additional antiretroviral effects of Viracept when combined with stavudine, it was also noted that this combination therapy was generally well tolerated. Diarrhoea and asthenia were the most frequent adverse events. When it occurred, diarrhoea was readily controlled, and the incidence of this side-effect decreased after the initial 60-day treatment period.

Clinical evaluations suggest that optimal efficacy and good patient tolerance are seen with Viracept 750 mg t.i.d.

Viracept reduces viral load and increases $CD4^+$ cell counts in HIV patients in a dose-related manner

FIGURE 3.2



Effect of switching from standard-dose stavudine monotherapy to therapy with stavudine plus Viracept: results from the 3-month extension to study 510; (a) effect on HIV-RNA; (b) effect on absolute CD4$^+$ cell count

Study AG1343-509

This phase II study investigated whether a triple-agent regimen of Viracept plus two nucleoside analogues can produce durable suppression of viral replication to below detectable levels. Twelve HIV-positive patients (antiretroviral naive) with HIV-RNA levels of greater than 10,000/ml were recruited into the study. Patients received Viracept, 750 mg t.i.d., plus zidovudine, 200 mg t.i.d., plus lamivudine, 150 mg b.i.d., for 12 weeks.

Plasma viral RNA was suppressed to below detectable levels (< 500 copies/ml) (Figure 3.3) and culture of peripheral blood monocytes was unsuccessful in detecting HIV-RNA in 11 patients (one patient withdrew – see below), suggesting marked suppression of viral replication by this triple combination. There was also an increase in CD4$^+$ cell count after 12 weeks of therapy of around 100 cells/mm^3 (mean, 109 cells/mm^3; median, 98 cells/mm^3).[30–32]

Although one patient withdrew from the study due to grade 4 elevation of plasma creatine phosphokinase levels and mild diarrhoea associated with abdominal cramping, this Viracept triple regimen was generally well tolerated, and many patients continued on therapy for 1 year,[33] enjoying sustained responses. At week 40, 10 of the 11 patients (91%) in the trial still had undetectable levels of HIV-RNA (assay detection limit, HIV-RNA > 500 copies/ml).[33]

Pivotal phase II/III studies

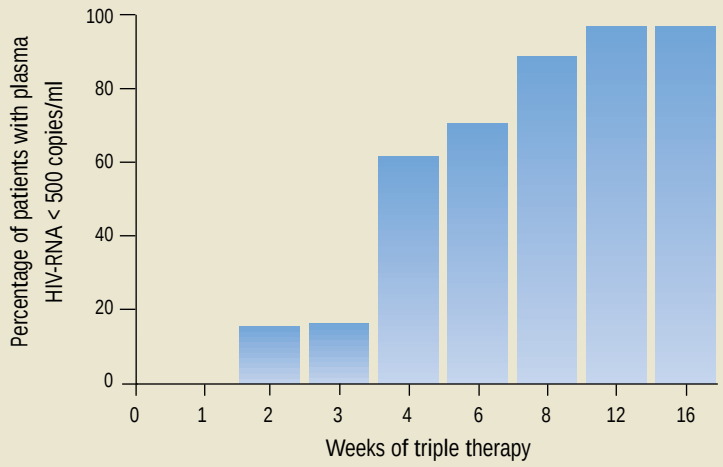
Following the positive findings of phase II studies, which showed Viracept to have potent antiretroviral effects, two doses of Viracept (500 mg t.i.d. and 750 mg t.i.d.) were chosen for further evaluation. Three pivotal studies have been performed: a monotherapy study (AG1343-505) to establish the Viracept dose–response relationship in HIV patients, and two combination therapy studies (AG1343-506 and AG1343-511). Descriptions and results from these three studies are provided below. In each of the studies, HIV-positive patients with CD4$^+$ cell counts ≥ 50/mm^3 and HIV-RNA levels ≥ 15,000/ml were enrolled. Randomization was stratified according to the duration of previous nucleoside analogue therapy (< 6 or ≥ 6 months), and CD4$^+$ cell count (≥ 50 to ≤ 300 or > 300 copies/mm^3).

Study AG1343-505

This study compared the doses of Viracept, 500 mg t.i.d. and 750 mg t.i.d. in 93 HIV-positive patients. Approximately 80% of patients had previously received antiretroviral therapy (mean duration, 27 months).

Treatment was divided into two stages: stage 1 of this study (4 weeks) was placebo-controlled and

FIGURE 3.3



Percentage of patients receiving triple therapy with Viracept, 750 mg t.i.d., zidovudine, 200 mg t.i.d. and lamivudine, 150 mg b.i.d., achieving viral suppression below detectable levels in study AG1343-509 (n =11)

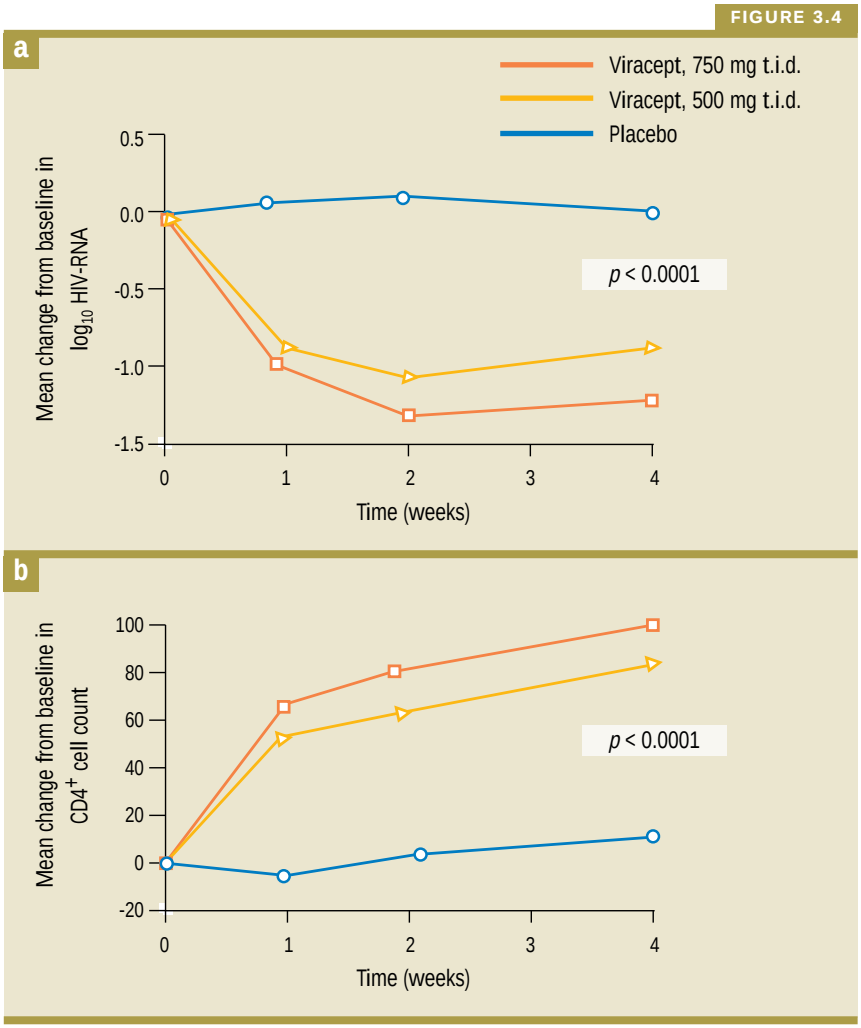
designed to demonstrate the efficacy of the two doses of Viracept. During stage 2 (20 weeks), all patients, including those previously given placebo, received Viracept.[34,35]

At both 500 mg and 750 mg t.i.d., Viracept produced significantly greater decreases in plasma HIV-RNA, compared with placebo ($p < 0.0001$) (Figure 3.4a). The mean area under the curve minus baseline (AUC_{MB}) log_{10} decreases were 1.019 for Viracept, 750 mg t.i.d., and 0.842 for Viracept, 500 mg t.i.d., compared with 0.026 for placebo ($p < 0.0001$). In addition, 10% and 16% of patients in the Viracept groups achieved HIV-RNA levels below the limit of detection between weeks 2 and 4, which was not seen in any patients in the placebo group.[35,36]

Viracept also produced a significant increase in $CD4^+$ cell count, compared with placebo ($p = 0.0001$) (Figure 3.4b). Mean AUC_{MB} increases in $CD4^+$ cell count for stage 1 were: 68 cells/mm^3 for Viracept, 750 mg t.i.d.; 55 cells/mm^3 for Viracept, 500 mg t.i.d.; and 3 cells/mm^3 for placebo.

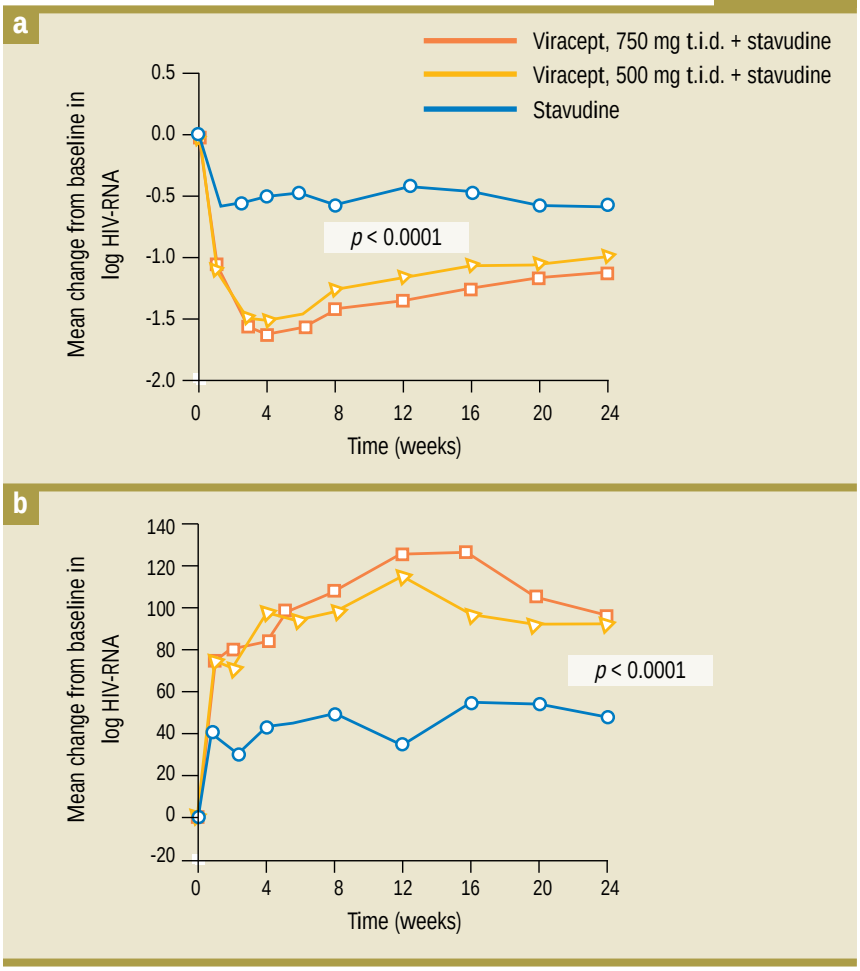
Stage 2 of the study revealed statistically significant differences between the two Viracept doses, with the higher dose producing greater suppression of HIV-RNA and bigger increases in $CD4^+$ cell count.

FIGURE 3.4



Mean changes in (a) HIV-RNA and (b) $CD4^+$ cell count achieved during Viracept monotherapy in study AG1343-505 (n = 93)

FIGURE 3.5



Mean change in a) HIV-RNA and b) CD4$^+$ cell count achieved during Viracept plus stavudine therapy in study AG1343-506 (n = 306)

The mean AUC_{MB} log_{10} (16 weeks) decrease in HIV-RNA was 0.928 for Viracept, 750 mg t.i.d., and 0.685 for Viracept, 500 mg t.i.d. Intention-to-treat analysis showed a statistically significant difference between the two Viracept treatment groups (p = 0.0410). Similarly, the mean AUC_{MB} (16 weeks) increases in CD4$^+$ cell count were: 87 cells/mm^3 for Viracept, 750 mg t.i.d.; and 60 cells/mm^3 for Viracept, 500 mg t.i.d. Intention-to-treat analysis again revealed a significant difference between the two treatment groups (p = 0.0227).[37,38]

This study found that both doses of Viracept were well tolerated. The most common adverse event seen with Viracept therapy was grade 2 or greater diarrhoea, but no statistically significant differences were noted, compared with placebo, or between the daily doses of Viracept.

Study AG1343-506

This study investigated Viracept at doses of 500 mg t.i.d. and 750 mg t.i.d. in combination with stavudine in a group of 306 HIV-positive patients who were naive to protease inhibitors, but zidovudine-experienced (two-thirds of the patients had received > 6 months of zidovudine treatment). Patients were randomized into three treatment groups, and the study was conducted over a 24-week period.

Patients received one of three regimens:

- Viracept, 500 mg t.i.d., *plus* stavudine (n = 97)
- Viracept, 750 mg t.i.d., *plus* stavudine (n = 101)
- placebo *plus* stavudine (patients < 60 kg, 30 mg b.i.d.; > 60 kg 40 mg b.i.d.) (n = 108)[39,40]

In keeping with the results of the phase II study (AG1343-510), addition of Viracept produced significantly greater improvements in viral load and CD4$^+$ cell count than seen with stavudine therapy alone (p < 0.0001) (Figure 3.5; for results of intention-to-treat analyses at 24 weeks, see Table 3.3). No significant differences were observed between the two doses of Viracept, with both being effective in this respect.[40]

Viracept had particularly marked effects on viral replication. The regimens employing Viracept together with stavudine were more effective than stavudine monotherapy in suppressing HIV-RNA to below the level of detection (< 500/ml). At the doses studied, Viracept allowed between 25% and 35% of patients to achieve a reduction in HIV-RNA to undetectable levels.[41]

The Viracept and stavudine combination was generally well tolerated, though diarrhoea (of grade 2 or greater) was increased by the addition of Viracept, compared with stavudine alone (Viracept 750 mg, 31%; Viracept 500 mg, 28%; placebo, 10%; p < 0.001).

These results show that the addition of Viracept to standard stavudine therapy causes a further and significant suppression of viral replication accompanied by significant increases in CD4$^+$ cell counts.

TABLE 3.3

Treatment group	HIV RNA (log_{10})				CD4$^+$ cell count			
	Mean AUCMB (log_{10} copies/ml)	*p* value			Mean AUCMB (cells/mm^2)	*p* value		
		Overall	Between treatments			Overall	Between treatments	
Study 506								
Viracept 750 mg + stavudine (*n* = 101)	–1.287	<0.0001	Viracept, 750 mg vs. stavudine alone	<0.0001	+96	<0.0001	Viracept, 750 mg vs. stavudine alone	<0.0001
Viracept 500 mg + stavudine (*n* = 97)	–1.213		Viracept, 500 mg vs. stavudine alone	<0.0001	+92		Viracept, 500 mg vs. stavudine alone	<0.0001
Stavudine alone (*n* = 108)	–0.573		Viracept, 750 mg vs. 500 mg	0.291	+42		Viracept, 750 mg vs. 500 mg	0.6251
Study 511								
Viracept 750 mg + zidovudine/lamivudine (*n* = 99)	–2.19	<0.0001	Viracept, 750 mg vs. zidovudine/ lamivudine	<0.0001	+109	0.0313	Viracept, 750 mg vs. stavudine alone	0.0285
Viracept 500 mg + zidovudine/lamivudine (*n* = 97)	–2.11		Viracept, 500 mg vs. zidovudine lamivudine	<0.0001	+108		Viracept, 500 mg vs. stavudine alone	0.05
Zidovudine/lamivudine alone (*n* = 101)	–1.52		Viracept, 750 mg vs. 500 mg	0.2811	+83		Viracept, 750 mg vs. 500 mg	0.8311

Intention-to-treat analysis of HIV-RNA and CD4$^+$ cell count AUCMB (24-week analysis) for studies AG1343–506 and 511

Study AG1343-511

This clinical study investigated a triple-agent combination of Viracept plus zidovudine plus lamivudine in 297 HIV-positive patients over an initial 24-week period. Patients entering the study were stratified according to CD4$^+$ cell counts (< 100; ≤ 100 to < 300; ≥ 300 cells/mm^3) and randomized to one of the three treatment regimens.[42]

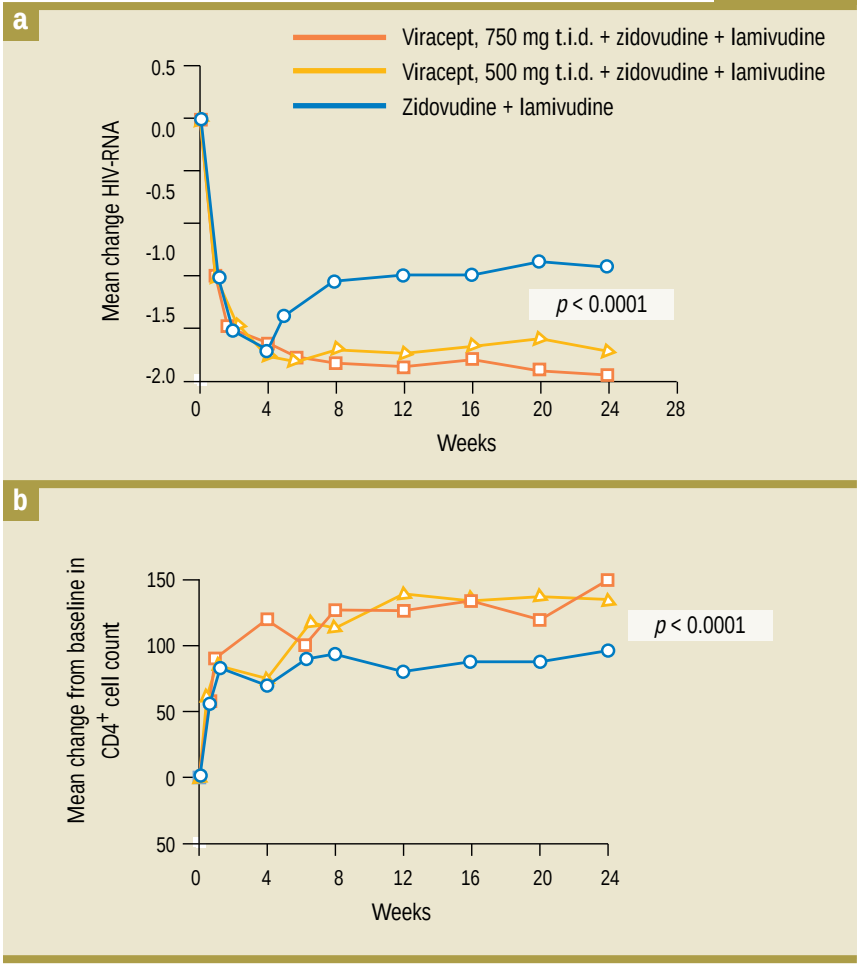
- Viracept, 500 mg t.i.d., *plus* zidovudine, 200 mg t.i.d., *plus* lamivudine, 150 mg b.i.d. (*n* = 97)
- Viracept, 750 mg t.i.d., *plus* zidovudine, 200 mg t.i.d., *plus* lamivudine, 150 mg b.i.d. (*n* = 99)
- Placebo *plus* zidovudine, 200 mg t.i.d., *plus* lamivudine, 150 mg b.i.d. (*n* = 101).

The median age of the patients was 35, with 89% male and 78% Caucasian. These patients had a mean baseline serum HIV-RNA level of 153,044 copies/ml and a mean baseline CD4$^+$ cell count of 288 cells/mm^3.[43]

The regimens that included Viracept were significantly more effective than zidovudine/lamivudine alone in reducing viral load (i.e. plasma viral RNA

The triple combination of Viracept plus two nucleoside analogues was effective in suppressing viral load

FIGURE 3.6



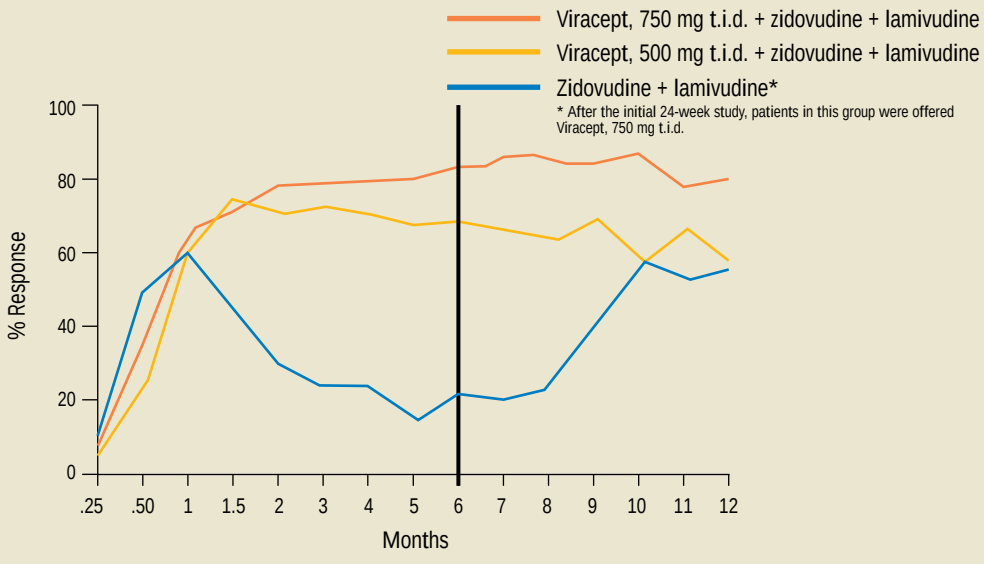
Mean change from baseline in (a) HIV-RNA and (b) CD4+ cell count achieved during Viracept plus zidovudine plus lamivudine therapy in study AG1343-511; data for the initial 24-week study period (n = 297). HIV-RNA was assessed using an experimental bDNA assay (sensitivity = 100 copies/ml)

levels) over the 24-week initial study period ($p < 0.0001$; Figures 3.6 and Table 3.3). The combination of Viracept with the two nucleoside analogues caused further significant increases in $CD4^+$ cell counts, which were sustained over the 24-week initial study period ($p = 0.03$; Table 3.3),[43] confirming the positive actions of Viracept on these two key surrogate markers of HIV disease progression.

The time to response, in terms of viral load reduction to HIV-RNA < 500 copies/ml, was rapid in patients receiving the Viracept triple combination, and was sustained over the treatment period. Furthermore, striking differences in the numbers of patients whose viral RNA fell below 500 copies/ml were observed between patients receiving Viracept and those given only zidovudine/ lamivudine. After 24 weeks of therapy, the proportion of patients with plasma HIV-RNA below 500 copies/ml were:

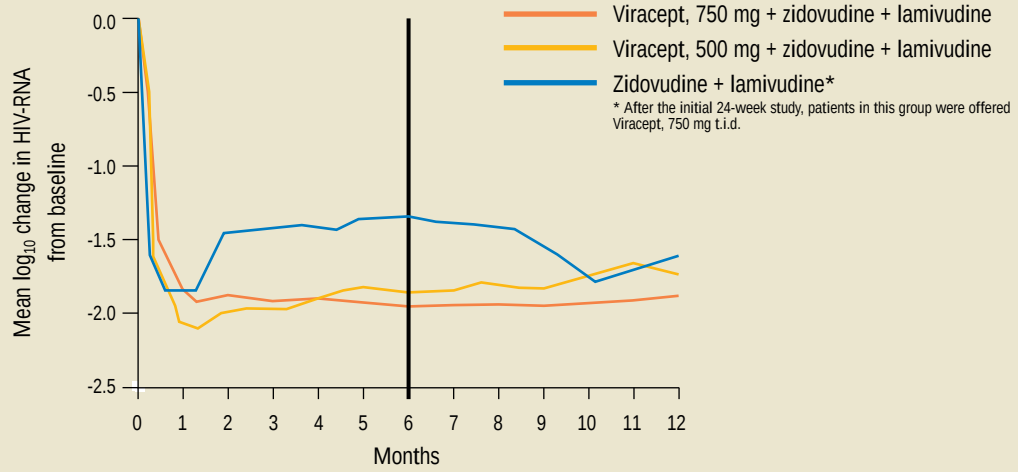
- 82% for Viracept, 750 mg t.i.d., *plus* zidovudine *plus* lamivudine
- 66% for Viracept, 500 mg t.i.d., *plus* zidovudine *plus* lamivudine
- 21% for zidovudine *plus* lamivudine (Figure 3.7).[43]

FIGURE 3.7



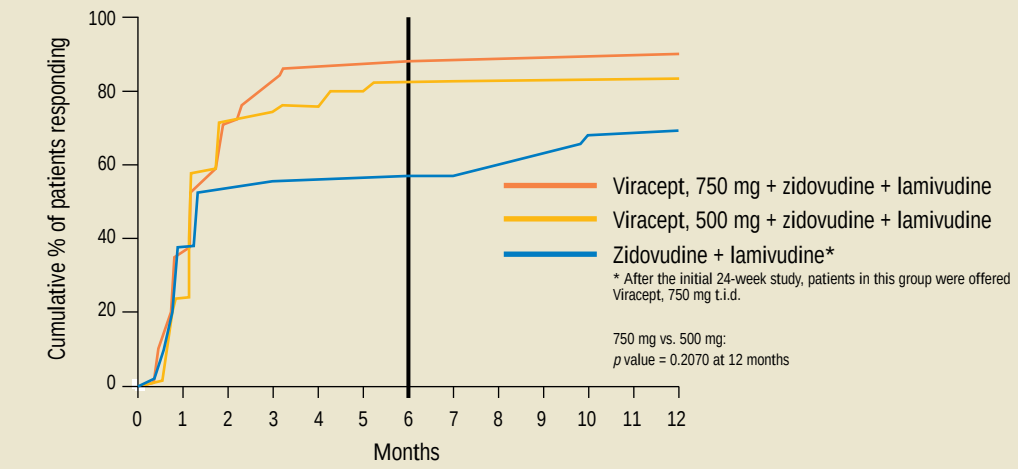
Percentage of patients (cumulative) with HIV-RNA below 500 copies/ml following treatment with a triple combination of Viracept, zidovudine and lamivudine in study AG1343-511

FIGURE 3.8



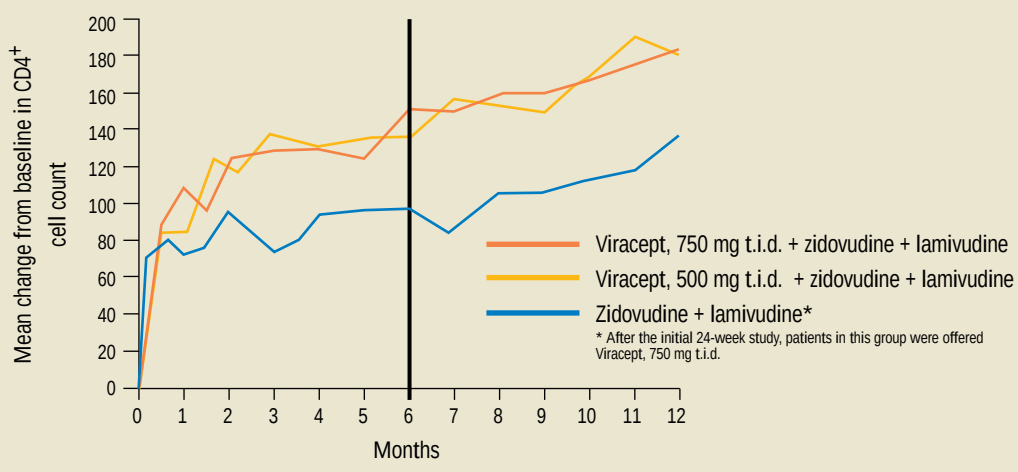
Reduction in log_{10} HIV-RNA over a 12-month (52-week) period in study AG1343-511 (assay sensitivity = 500 copies/ml)

FIGURE 3.9



Time to response and duration of response (decrease in HIV-RNA to below 500 copies/ml with confirmation) in study AG1343-511

FIGURE 3.10



Change in $CD4^+$ cell count from baseline over a 12-month (52-week) period in study AG1343-511

TABLE 3.4

Visit	n	Log_{10} HIV-RNA (PCR) change from baseline	Percentage of patients below level of detectability (< 400 copies/ml)
Week 4	9	–2.01	11%
Week 8	9	–2.48	78%
Week 12	9	–2.62	89%
Week 16	9	–2.73	100%

Mean baseline HIV-RNA (PCR) = 194,814 (5.29 log_{10})

Change in HIV-RNA levels from baseline following treatment with Viracept, 1250 mg b.i.d., combined with stavudine, 30/40 mg b.i.d., plus lamivudine, 150 mg b.i.d., in HIV-positive patients naive to antiretroviral medication.

CD4+ cells showed a continuous rise from baseline over 12 months in patients receiving a Viracept-containing triple-combination regimen

At 24 weeks of therapy, 82% of patients receiving Viracept triple-combination regimen had HIV-RNA levels below 500 copies/ml

Continuation to 52 weeks – sustained benefits from Viracept in combination

Study AG1343-511 was extended, with data available for 52 weeks of combination therapy (Viracept plus zidovudine plus lamivudine).[44] After 24 weeks, patients initially receiving zidovudine plus lamivudine were offered Viracept, 750 mg t.i.d. Over the entire period of the study, patients receiving the triple combination showed a sustained response to therapy (Figure 3.8). It was found that the mean reduction in viral load was sustained over 52 weeks, with 80% of patients in the Viracept, 750 mg t.i.d., group still found to have plasma HIV-RNA levels below 500 copies/ml (Figure 3.7). The reduction in HIV-RNA was analysed by two methods – one the bDNA method (detection limit 500 copies/ml) and the other, the Amplicor®-PCR method (detection limit 400 copies/ml). This reduction in viral load was sustained over the study period and the decrease in viral load was statistically significant for both of the Viracept treatment arms (Figure 3.9).

The $CD4^+$ cell count continued to increase from baseline over 52 weeks of therapy. Patients receiving Viracept showed a mean increase above baseline of 150 cells by 6 months, increasing to 180 cells above baseline after 12 months of therapy (Figure 3.10).

By the end of 1 year of treatment with Viracept plus zidovudine plus lamivudine, a general decrease in the incidence of adverse events was seen,[44] confirming the good safety profile of Viracept in clinical use.

Maximum viral suppression is a key goal of antiretroviral therapy. By 12 months, more than 80% of patients receiving Viracept, 750 mg t.i.d., continued to respond to treatment – a figure statistically different from the 12-month response in patients receiving Viracept, 500 mg t.i.d. On the basis of these study findings, Viracept, 750 mg t.i.d., is now the recommended dose for use in adults with HIV disease.

Viracept dose and treatment outcome

Analysis of response according to stage of disease revealed that patients with more advanced disease were more likely to benefit from a higher dose of Viracept. For example, of the patients with baseline $CD4^+$ cell counts $\leq$ 50, the percentage in each treatment group achieving viral suppression to below detectable levels (< 500/ml) after 24 weeks of therapy was:

- 73% of patients receiving the combination with Viracept, 750 mg t.i.d.
- 38% of patients receiving the combination with Viracept, 500 mg t.i.d.[44]

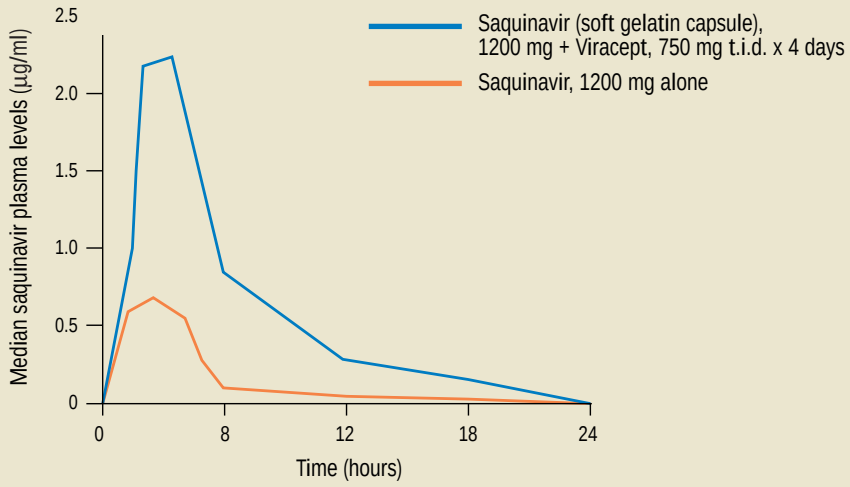
Viracept – other clinical studies

Viracept b.i.d. study

Although currently recommended as a therapy that should be given three times a day, Viracept has a plasma half-life of 3.5–5 hours, which may allow for twice-daily dosing. Interim results from an open-label study in 10 patients who received a 1250 mg b.i.d. regimen of Viracept combined with stavudine, 30/40 mg b.i.d., plus lamivudine, 150 mg b.i.d., suggest that this regimen may be as well tolerated and as effective as the Viracept, 750 mg t.i.d., regimen in combination.[45]

The study involved a small cohort of antiretroviral-naive, HIV-positive patients and was designed to examine, over a 24-week period, the effect of the Viracept b.i.d. triple combination regimen on plasma HIV-RNA levels (detection limit 400 copies/ml), $CD4^+$ count, patient compliance and tolerability of the regimen.

FIGURE 3.11



Effect of a combination of Viracept and saquinavir (soft gelatin capsule, Fortovase®) on median plasma levels of saquinavir

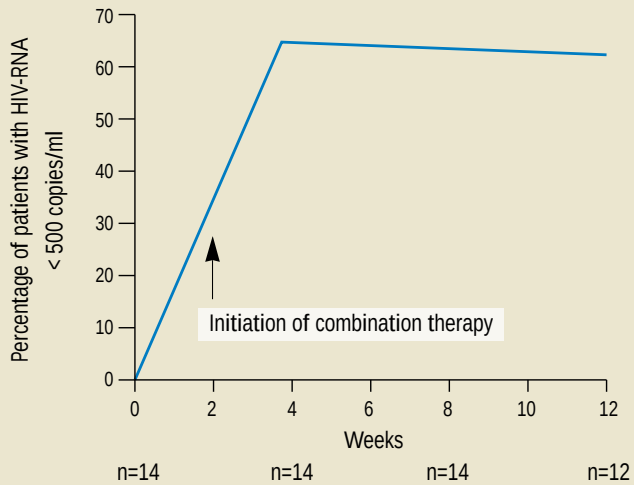
Results analysed at 16 weeks show that Viracept b.i.d. in combination with two nucleoside analogues reduced viral load measurements by more than 2.5 $\log_{10}$ and to below the level of detectability in all 9 patients assessed (Table 3.4). The mean $CD4^+$ cell count rose to 415 cells/mm^3, representing an increase of 75 cells/mm^3.

A large multicentre European study in progress will evaluate further the Viracept b.i.d. regimen in combination with nucleoside analogues.
Preliminary results suggest that the efficacy and tolerability of Viracept, 1250 mg b.i.d., was comparable to the 750 mg t.i.d. regimen.[46]

Viracept in combination with other protease inhibitors

The role of Viracept in combination with other protease inhibitors has been explored in two related clinical studies to date; one of which sought to determine the single- and multiple-dose pharmacokinetics of Viracept and saquinavir soft-gel capsule (SGV-SGC, Fortovase®) in combination;[47] and a second follow-on study that will determine the efficacy of this same combination of protease inhibitors in terms of effect on viral load and $CD4^+$ cell count (Study on Protease Inhibitor Combination in Europe [SPICE] study).[48]

FIGURE 3.12



Proportion of patients with HIV-RNA levels below 500 copies/ml following treatment with a combination of Viracept and saquinavir SGC (Fortovase®)

In the single and multidose pharmacokinetic study,[47] 14 patients already receiving nucleoside therapies, were enrolled in a two-way, randomized cross-over study. The pharmacokinetics of single doses of Viracept, 750 mg, or saquinavir SGC, 1200 mg, were evaluated prior to and on the last day of a 4-day regimen of the other protease inhibitor (saquinavir SGC, 1200 mg t.i.d., or Viracept, 750 mg t.i.d.). Treatments were then reversed after a 3–10 day wash-out.

Preliminary studies in children with HIV infection suggest that Viracept is a well-tolerated and effective antiretroviral drug

By 12 months (52 weeks) on Viracept (at the recommended dose) triple-combination therapy, 80% of patients had HIV-RNA levels below 400–500 copies/ml

Results from this study found that Viracept increased saquinavir single-dose exposure 5-fold (Figure 3.11). In contrast, saquinavir had little effect on the Viracept single-dose pharmacokinetics. Preliminary results from this study also suggest that Viracept in combination with saquinavir SGC (Fortovase®) has a good efficacy profile, as suggested by the percentage of patients in whom HIV-RNA fell below 500 copies/ml (Figure 3.12).

The SPICE study has been designed to evaluate the long-term safety, tolerance and anti-HIV activity of saquinavir SGC (Fortovase®) plus Viracept in 157 protease-naive patients. The study will compare four study arms: saquinavir SGC (plus nucleosides); Viracept (plus nucleosides); saquinavir SGC plus Viracept (plus nucleosides); saquinavir SGC plus Viracept without nucleosides.

Preliminary results suggest that the combination of saquinavir SGC and Viracept is generally well tolerated and has positive effects on viral load.[48]

Detailed information on the pharmacokinetic interactions of Viracept with other protease inhibitors can be found in Chapter 7.

Clinical studies in children

The paediatric formulation of Viracept has been studied in small groups of children with HIV, and the results suggest that this treatment has the same potential clinical benefits that have been noted in adults.

In a small pilot study, the effects of Viracept plus two nucleoside analogues were examined in a cohort of 10 infants younger than 1 year of age, with vertically transmitted HIV infection.[49] Data from four infants who received a combination regimen of Viracept plus zidovudine plus lamivudine for a period of 14 weeks suggest that this combination is well tolerated and results in reductions in viral load to undetectable levels.

Viracept – use in clinical practice

Ongoing clinical investigations will look at the role of Viracept in different combinations and in a variety of patient subgroups.

In clinical practice, the choice of agents selected for use in combination with Viracept always depends on the patient's antiretroviral drug history. However, as the results in this chapter and in Chapter 5 (which focuses on viral resistance) indicate, Viracept can be considered an ideal first-line choice of protease inhibitor.

Summary

Viracept has been the subject of extensive clinical study, showing potent antiretroviral activity in HIV infected patients. At a dose of 750 mg t.i.d., Viracept has been shown to be a highly effective and well-tolerated protease inhibitor, which, when used in combination with nucleoside analogues, suppresses viral replication to levels below the current limit of assay detection (i.e. < 400–500 copies/ml). Viracept therapy is also associated with persistent improvements in $CD4^+$ cell count.

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4 Safety and tolerance

The safety profile of Viracept (nelfinavir mesylate) has been assessed extensively in HIV-positive patients at different stages of disease progression. To date, over 800 HIV-positive patients have been exposed to Viracept during clinical studies, of which more than half received a dose of 750 mg t.i.d., either alone or in combination with nucleoside analogues. Over 4000 patients aged 13 years or older in the expanded access programmes received Viracept at a dose of 750 mg t.i.d. Viracept has been well tolerated generally. Although mild-to-moderate diarrhoea is the most frequently reported adverse event, this has been shown to be a manageable side-effect. Importantly, Viracept does not share the adverse events of nausea that have been associated with other protease inhibitors.

The safety and tolerance profile of Viracept at the recommended dose has been assessed in over 4000 patients in clinical studies and expanded access programmes

Adverse events

Adverse experiences of moderate to severe intensity, reported by investigators as at least possibly related to Viracept or of unknown relationship in ≥ 2% of patients treated with the 750 mg t.i.d. dose of Viracept (n = 243), alone or in combination with nucleoside analogues (for up to 24 weeks), have been assessed across the three double-blind studies (505, 506 and 511). These included the following undesirable side-effects: diarrhoea (25.1%), flatulence (3.3%), nausea (4.9%) and rash (2.9%).[1]

Diarrhoea

Mild-to-moderate diarrhoea is the most commonly observed adverse event associated with Viracept treatment, but is readily managed. Furthermore, the grade and rates of diarrhoea observed during Viracept therapy are not so severe as to be associated with weight loss.

In the double-blind studies, diarrhoea of grade 2 or greater was observed in 46 of 243 patients (18.9%) treated with Viracept 500 mg t.i.d. and in 61 of 243 patients (25.1%) of patients who received 750 mg t.i.d. There was no significant difference in the incidence of grade 2 or greater diarrhoea between the 500 mg and 750 mg t.i.d. Viracept doses (p = 0.266). This is comparable to the incidence of diarrhoea reported for the protease inhibitor ritonavir (18.3%),[2] and for other antiretroviral agents, such as zidovudine (22%). Diarrhoea associated with Viracept is rarely associated with nausea, vomiting or abdominal pain and is managed effectively with antidiarrhoeal agents.[2,3] Only 11 of the 696 patients enrolled in the double blind studies withdrew from studies because of diarrhoea.

Although formal analysis of the time to onset of diarrhoea were not performed, results from study 505 indicate that onset of diarrhoea generally occurs shortly after beginning treatment with Viracept and that new episodes of diarrhoea are unlikely to occur in patients who have been receiving Viracept for long periods of time and, in general, diarrhoea improves over time.

Clinical trials also found that Viracept combination therapy was not associated with a higher incidence of diarrhoea than Viracept monotherapy. In combination with zidovudine plus lamivudine, Viracept produced significantly less diarrhoea (≥ grade 2; 20 of 99 patients) than a combi-

TABLE 4.1

	Study 505		Study 506			Study 511			Studies 505, 506, 511	
	NFV $_{750}$ (n = 43)	NFV $_{500}$ (n = 48)	NFV $_{750}$+ D4T (n = 101)	NFV $_{500}$+ D4T (n = 98)	Placebo + D4T (n = 109)	NFV $_{750}$+ AZT+3TC (n = 99)	NFV $_{500}$+ AZT+3TC (n = 97)	Placebo + AZT+3TC (n = 101)	NFV $_{750}$ (n = 243)	NFV $_{500}$ (n = 243)
Diarrhoea	23	13	31	28	10	20	13	3	25.1	18.9
Flatulence	7	0	3	8	4	2	5	0	3.3	5.3
Nausea	7	0	2	3	1	7	3	4	4.9	2.5
Asthenia	2	2	1	3	4	1	1	2	1.2	2.1
Rash	2	4	3	4	0	3	1	1	2.9	2.9
Patients with at least one marked abnormal laboratory value	2	8	7	10	3	10	15	15	7.4	11.9
Neutrophils	0	2.1	4	1	0	3	3.1	4	2.9	2.1
Lymphocytes	0	0	0	1	0.9	0	5.2	1	0	2.5
ALT (SGPT)	0	2.1	2	3.1	0.9	1	1	5	1.2	2.1
Creatine kinase	2.3	0	5.9	4.1	2.8	1	2.1	5.9	3.3	2.5

NFV$_{750}$, Viracept 750 mg t.i.d.; NFV $_{500}$, Viracept 500 mg t.i.d.; AZT, zidovudine; D4T, lamivudine

Percentage of patients experiencing drug-related treatment-emergent adverse events of at least grade 2 severity in the double-blind studies (505, 506 and 511) during the pre-switch period (only events experienced in over 2% of patients are reported)

nation of Viracept and stavudine (31 of 101 patients; p = 0.015). These differences should be taken into consideration when selecting the most appropriate reverse transcriptase inhibitors (nucleoside analogues) for combination with Viracept.[3,4]

Other adverse events

Few other adverse events are associated with Viracept treatment. In the pivotal phase II/III studies, for example, flatulence, nausea, rash and asthenia of grade 2 or greater were reported in fewer than 4% of patients. Other events were less frequent. Table 4.1 lists the adverse events of grade 2 or greater reported in the pivotal studies.[3]

Serious adverse events and withdrawals from therapy

Only three deaths occurred during clinical studies, and none of these was considered to be related to Viracept treatment. Serious adverse events occurred during treatment in 5.6% (39) of patients involved in the pivotal phase II/III trials, but only 0.6% (4 events) of these were judged to be drug-related.[4,5]

Approximately 11% (77/696) of patients withdrew from the double-blind clinical studies. In only 28 cases (4% of patients) was withdrawal due to treatment-emergent adverse events. Diarrhoea was the most common cause of treatment-emergent withdrawals (11 patients) (Table 4.2). Withdrawal was not related to the dose of Viracept received (p = 0.176). Importantly, withdrawal rates were not significantly different for Viracept combination therapy versus control therapy (i.e. stavudine, or zidovudine plus lamivudine) (p = 0.555), or Viracept combination therapy *versus* Viracept monotherapy (p = 0.108).[5]

Clinical laboratory results

The incidence of marked clinical laboratory abnormalities (i.e. change from zero to grade 3 or 4, or a change from grade 1 to grade 4) in double-blind studies was 7.4% (18 out of 243 patients) in patients receiving Viracept, 750 mg t.i.d. and

11.9% (29 out of 243 patients) in patients receiving Viracept 500 mg t.i.d. (see also Table 4.1).[1] No relationship between the dose of Viracept and the incidence of such abnormalities was evident. Some of these abnormalities are likely to reflect the effects of other agents involved in the combined regimens. For example, most of the haematological changes observed in study 511 (Viracept plus zidovudine plus lamivudine) were consistent with those seen in patients receiving the combined regimen of zidovudine plus lamivudine. Marked clinical laboratory abnormalities reported in 2% or more of patients treated with Viracept, 750 mg t.i.d., for up to 24 weeks included increases in creatine kinase (3.3%) and decreased neutrophils (2.9%). Marked increases in transaminases occur in less than 2% of patients receiving Viracept at the recommended dose of 750 mg t.i.d. In all three studies, most patients who experienced abnormalities in liver function had a previous history of hepatitis and/or alcohol abuse.[1,6]

Comparisons with other protease inhibitors

The safety and tolerability profile of Viracept compares favourably with that of ritonavir and indinavir, and is comparable with that of saquinavir. Indinavir has been associated with nephrolithiasis (4–10% of patients). Other side-effects of these drugs include nausea, vomiting and headache. For example, the combination of indinavir plus zidovudine was associated with the following adverse events of grade 2 or greater: nausea in 32% of patients, vomiting in 12%; headache in 12%.[7]

At high peak plasma concentrations of the protease inhibitor ritonavir, severe adverse events (e.g. nausea, asthenia, vomiting and taste perversion) have been observed; titration of this drug is recommended to avoid these unwanted effects. In combination with zidovudine, ritonavir is associated with nausea (47% of patients), asthenia (28%), vomiting (22%) and taste perversion (16%). These adverse events are thought to contribute to the high withdrawal rates seen in some ritonavir studies (e.g. 40% in study 245).[7]

TABLE 4.2

Adverse event	Percentage of patients (n)
Diarrhoea	1.6 (11)
Nausea	1.1 (8)
Flatulence	0.6 (4)
Asthenia	0.6 (4)
Vomiting	0.4 (3)
Headache	0.4 (3)

Most commonly reported adverse events leading to discontinuation of treatment during double-blind studies (505, 506 and 511)

Viracept is generally well tolerated

The adverse event profile of Viracept has more in common with that reported for saquinavir, which has mild, low-frequency side-effects, such as diarrhoea, nausea and abdominal pain, when used alone and in combination with zidovudine, zalcitabine or both. For example, a study of saquinavir and zalcitabine in combination found that diarrhoea was the most frequent adverse event (3.8%), while moderate fatigue was the commonest adverse event (17%) seen with triple-agent therapy (saquinavir plus zalcitabine plus zidovudine).[8]

The incidence of grade 2 diarrhoea with Viracept therapy is comparable to that seen with other antiretroviral agents and is easily managed

Comparison of all four available protease inhibitors suggests that Viracept and saquinavir are equally well tolerated by patients, and have side-effects that are easily managed in clinical practice. These agents appear to have the most favourable safety and tolerability profile, with Viracept displaying characteristics desirable in a first-line therapy.

Tolerance in children

Preliminary studies in children have shown that Viracept is well tolerated.[9] The overall incidence of diarrhoea reported in these studies seems to be lower than that reported for adults.[9,10] No serious adverse events have been reported in children. These data suggest that Viracept could have a valuable role in the treatment of children with HIV disease.[10,11]

Summary

The safety and tolerability of Viracept at the recommended dose has been assessed in approxi-

The safety profile of Viracept compares favourably with that of ritonavir and indinavir and is comparable to that of saquinavir

Viracept appears to be well tolerated in children

mately 400 patients in clinical studies and in over 4000 patients through expanded access programmes.

Viracept is a generally well-tolerated protease inhibitor that has a favourable safety profile. Few side-effects are associated with treatment. Clinical experience with the drug shows that it compares favourably with established protease inhibitors in terms of safety and tolerability.

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5 Resistance

In choosing Viracept (nelfinavir mesylate), clinicians select a drug with potent antiretroviral activity. Used in combination with reverse transcriptase inhibitors, Viracept has been shown to suppress viral replication to undetectable levels. These marked effects on viral replication are known to translate into clinical benefit for patients. A further advantage of this potent antiretroviral activity is that viral replication is suppressed to a point where the potential for emergence of viral strains that are resistant to Viracept and other protease inhibitors is greatly reduced. Evidence from clinical studies supports the notion that decreased sensitivity, or resistance, to Viracept (when used in a combination regimen able to suppress viral replication effectively) is rare. In vitro and in vivo investigations have sought to identify and understand the processes and conditions that would select for resistance to Viracept.

Viracept is a potent antiretroviral agent, which in combination with reverse transcriptase inhibitors is capable of suppressing viral replication to below the level of quantification

Introduction

Resistance to antiretroviral agents represents a major threat to successful treatment of HIV disease and in the past has been responsible for many treatment failures. With the advent of new combination regimens, which cause marked suppression of viral replication, it is hoped that greater control will be exerted on the emergence of HIV variants that show decreased sensitivity or marked resistance to clinically effective antiretroviral agents.

The issue of antiretroviral resistance has become almost as crucial as efficacy when selecting agents for use in the management of HIV disease. It appears that the emergence of resistance to drugs can be delayed, if not completely overcome, by appropriate treatment strategies that achieve effective control of virus turnover. The use of combinations of drugs that, together, cause powerful suppression of viral replication (to the extent that plasma HIV-RNA cannot be detected by sensitive, ideally ultrasensitive, assays) offers the best strategy in controlling the emergence of resistance. Limited cross-resistance data, generated by *in vitro* and *ex vivo* studies, suggests that patients who develop viral resistance to Viracept might benefit from subsequent treatment with other protease inhibitors. In this respect, Viracept offers an improved profile over the existing protease inhibitors, as it has marked antiretroviral activity and appears to have a low potential to induce cross-resistance to other protease inhibitors.

In attempting to define the potential for decreased sensitivity and viral resistance to agents such as Viracept, a number of investigative approaches are employed.

Altered susceptibility to an antiretroviral agent is a phenomenon that can be studied both *in vivo* and *in vitro*. Studies have therefore been made of the susceptibility of HIV isolates obtained from patients who have been exposed to clinical treatment with Viracept; in addition, *in vitro* experiments have been performed on HIV cultures to determine the nature of phenotypic and genotypic resistance that could occur during viral exposure to Viracept.

Resistance to Viracept

In vitro studies

Serial passaging of HIV in cell culture in the presence of nelfinavir led to the isolation of an HIV vari-

Viracept, in combination with nucleoside analogues, curbs viral replication to a point that limits the emergence of HIV variants resistant to this drug

ant (at passage 22) that exhibited a 9-fold reduced sensitivity to Viracept.[1] Sequencing of the protease gene from this p22-variant revealed a unique substitution of aspartic acid by asparagine at residue 30 of the protease enzyme (D30N). This substitution has not been seen previously in HIV isolates that are resistant to other protease inhibitors. Thus, the development of reduced sensitivity to Viracept *in vitro* appears to occur by a pathway distinct from resistance to the other protease inhibitors.[2]

Clinical studies

Virus isolates obtained from patients who received Viracept during the course of clinical studies were studied *in vitro* and were found to display the characteristic genotypic patterns associated with decreased sensitivity to Viracept. As predicted by the *in vitro* data described above, the most common genotypic mutation in the HIV protease gene that emerged *in vivo* was the D30N substitution.

TABLE 4.2

Genotypic change	Prevalence in % (no. of pts)	
	Baseline (n=55)	After Viracept treatment (n=55)
D30N (aspartic acid to asparagine)	0.0 (0)	45.5 (25)
E35D (glutamic acid to aspartic acid)	21.8 (12)	32.7 (18)
M361 (methionine to isoleucine)	27.3 (25)	41.8 (23)
M461 (methionine to isoleucine)	0.0 (0)	12.7 (7)
A71T/V (alanine to theronin/valine)	7.3 (4)	23.6 (13)
V771 (valine to isoleucine)	27.3 (15)	40.0 (22)
N88S/S (asparagine to aspartic acid/serine)	0.0 (0)	20.0 (11)

Predominant genotypic changes in HIV-RNA from patients treated with Viracept in studies 503 and 510

Sequence analyses of HIV protease genes were performed on viral RNA isolated from 58 patients enrolled in phase I/II studies – study 503 (Viracept monotherapy, dose-escalation study) and 510 (Viracept plus stavudine study). Sequence analyses were performed at baseline and after a median of 13 weeks (range 3–52 weeks) of study treatment. The patients sampled had displayed a variety of virological responses, ranging from sustained viral load reductions to HIV-RNA levels returning to baseline values. The predominant mutation in this group of patients receiving either Viracept monotherapy or Viracept in combination with stavudine was at amino acid position 30 (D30N), which was detected in 45.5% of patients. This substitution was maintained in a subset of these patients, followed for up to 44 weeks. Mutations described for other protease inhibitors were either never observed (G48V, V82F/T, I84V) or only rarely observed (mutation L90M; 3 of 55 patients) (Table 5.1).[3]

Of the 20 patients from phase I/II studies 503 and 510 in whom phenotypic and genotypic analyses of clinical isolates were performed, 10 patients showed reduced phenotypic susceptibility (5- to 93-fold) to Viracept *in vitro* (defined as a > 5-fold decrease in EC_{90}, compared with baseline). All 10 patients presented one or more mutations in the virus protease gene, with amino acid position 30 being the most commonly involved mutation site. In contrast, none of the 10 viral isolates that showed full sensitivity to Viracept *in vitro* displayed the D30N genotypic mutation.[4]

Further analyses exploring the resistance profile of Viracept were performed in the context of pivotal phase II/III studies. Genotypic sequencing analyses were performed in a randomly selected sample of 142 patients from study 505 (Viracept 500 mg t.i.d. or 750 mg t.i.d. as monotherapy) and study 511 (Viracept 500 mg t.i.d. or 750 mg t.i.d. plus zidovudine plus lamivudine *versus* zidovudine plus lamivudine).

Amino acid position 30 appeared to be the most frequent mutation site in this patient sample, confirming the genotypic mutation profile described in phase I/II studies. The D30N mutation was detected after 12–16 weeks of treatment in 56% of patients (36/64) receiving Viracept monotherapy (study 505) – an incidence comparable to the findings in phase I/II studies. In contrast, only 3 out of 49 patients (6%) receiving Viracept in combination with zidovudine and lamivudine developed the D30N mutation after 12–16 weeks of treatment.[1,4]

The N88D/S mutation was rarely observed in patients receiving Viracept monotherapy and was never observed when Viracept was used in combination with zidovudine and lamivudine. Similarly, the L90M mutation was observed in 8% (5/64) of patients receiving Viracept monotherapy, but was never seen in individuals treated with triple-combination therapy. Mutations typically associated with resistance to other protease inhibitors, such as the G48V, V82A/F/T or I84V mutations, were not observed in either the monotherapy or the triple-combination therapy groups.[3,5]

Thus, results from phase II/III studies showed a dramatic reduction in the incidence of genotypic mutations in the group of patients who received Viracept in combination with two nucleoside analogues, as compared with patients who received Viracept monotherapy.

These findings support the hypothesis that combination regimens that are highly effective in suppressing viral replication and in controlling virus turnover, reduce the likelihood of emergence of viral mutants associated with drug resistance.

In conclusion, highly suppressive antiretroviral combinations containing Viracept seem to prevent or delay the development of resistance.

In vitro sensitivity of Viracept-resistant virus to other protease inhibitors

Viracept-resistant viruses were produced *in vitro* by serial passaging of HIV with increasing concentrations of Viracept. The predominant genotypic mutation found in these studies was D30N. Since mutation at position 30 is key to the development of resistance to Viracept but does not overlap with previously identified mutations for other protease inhibitors, it was suggested that Viracept-resistant mutants may not be cross-resistant to other protease inhibitors.[6]

When the susceptibility of *in vitro*-derived Viracept-resistant HIV was assessed, the virus remained fully sensitive to saquinavir, ritonavir, indinavir and 141W94.[7] Six isolates containing the D30N substitution, which were obtained from patients enrolled in Viracept clinical trials, showed no reduced sensitivity to saquinavir, ritonavir, indinavir and 141W94 *in vitro*.[1,4,7] This lack of *in vitro* cross-resistance was confirmed in studies involving a recombinant virus containing the D30N substitution; the recombinant virus exhibited a reduced sensitivity to Viracept, yet retained full sensitivity to other protease inhibitors.

These *in vitro* findings suggest that HIV variants with reduced susceptibility to Viracept remain sensitive to other protease inhibitors. The clinical relevance of the *in vitro* and *in vivo* genotypic and phenotypic changes associated with Viracept therapy has not yet been established.

Limited data suggest that patients who fail Viracept treatment due to the development of resistance have, in some cases, benefited from subsequent treatment with other protease inhibitors.

Preliminary data[8] suggest that saquinavir-experienced patients, who fail Viracept treatment, respond to indinavir and nevirapine. In contrast, an observational study,[9] which included 22 patients who had failed Viracept treatment, showed smaller than expected reductions in HIV-RNA when patients were switched to regimens containing indinavir or saquinavir plus ritonavir.

An additional observational study[10] conducted in 12 patients, showed that the patients failing on Viracept had a good clinical response to a combination regimen containing saquinavir, ritonavir, lamivudine and stavudine. In all 12 patients, HIV-RNA in plasma fell below the limit of quantification (500 copies/ml). In a second group of extensively pretreated patients who had received Viracept in a clinical trial, viral load was reduced below the level of quantification in three of seven patients after a switch to a quadruple regimen containing saquinavir, ritonavir, lamivudine and stavudine.

These limited data, generated in observational studies of relatively short duration, suggest that patients who fail on Viracept-containing regimens

Highly suppressive antiretroviral combinations containing Viracept seem to prevent or delay the development of resistance

HIV isolates that display resistance to Viracept are known to show genotypic changes quite distinct from those that emerge to other protease inhibitors

Viracept appears to have a low potential to induce cross-resistance to other protease inhibitors

Limited clinical data suggest that a proportion of patients who have failed on other protease inhibitors may benefit from Viracept

due to the development of resistance are not precluded from successful, subsequent treatment with other protease inhibitors. However, heavily pretreated patients may be less likely to have a robust and durable response.

Sensitivity to Viracept: virus resistant to other antiretrovirals

Cross-resistance between Viracept and nucleoside analogues is unlikely because of the different enzyme targets involved. HIV isolates resistant to nucleoside analogues and non-nucleoside analogues remain susceptible to Viracept *in vitro*. *In vitro* studies of 23 HIV isolates from patients failing treatment with indinavir, ritonavir or saquinavir found that 15 isolated variants (65%) had key mutations, or displayed phenotypic resistance to the protease inhibitor to which they had been exposed *in vivo*. Fourteen (61%) of the isolates were sensitive to Viracept *in vitro*; and 6 of the 15 isolates that presented only one key mutation associated with decreased sensitivity to the protease inhibitor used *in vivo*, were found to be fully susceptible to Viracept.[11,3]

The clinical relevance of these *in vitro* findings remains to be established. Limited clinical data suggest that patients who have failed other protease inhibitors might benefit from subsequent treatment with Viracept.

Preliminary data from a group of 43 extensively pretreated patients suggest that in this patient population, virologic responses to Viracept might be very variable. Patients in this observational study had been exposed to various nucleoside analogues and protease inhibitors. They were switched to a regimen containing Viracept, stavudine and didanosine, substances to which none of the patients had been previously exposed. After 12 weeks of therapy, 9 of 29 (31%) patients had plasma HIV levels below the level of quantification (500 copies/ml), while 7 of the 29 patients had no changes in HIV-RNA or increased HIV-RNA levels.[12]

Another observational study[13] explored the efficacy of Viracept in patients who failed or were intolerant to other protease inhibitors. Patients received Viracept, 1250 mg b.i.d., in combination with saquinavir hard gelatin capsule (1000 mg b.i.d.) and two nucleoside analogues. After 8 weeks of treatment, 10 of 17 patients (59%) had HIV-RNA plasma levels below the level of quantification (500 copies/ml). The median decrease in viral load was 1.8 $\log_{10}$; $CD4^+$ cell counts increased by 113 cells/mm^3.

The limited clinical data available suggest that in patients who have failed on other protease inhibitors, Viracept-containing combination regimens produced variable virologic responses, ranging from complete inhibition of viral replication to no evident response. This variability in treatment outcome could be explained by multiple factors, such as the degree of compensatory changes in the protease gene, mutations in the reverse transcriptase gene, degree of immunosuppression, and general difficulties in adhering to treatment. The virological and immunological characteristics associated with an optimal response to Viracept treatment in patients who had failed other protease inhibitors are not yet available. Available data suggest, however, that in a sub-group of patients who have failed on other protease inhibitors, Viracept-containing regimens produce treatment outcomes comparable to those observed in protease-inhibitor-naive patients.

Adherence to treatment – crucial factor in avoiding development of resistance

Another important factor that has been associated with the development of resistance to antivirals is lack of adherence to treatment schedule. This statement is valid with respect to antiretroviral treatment in general and Viracept treatment in particular. Subtherapeutic drug levels caused by dosage reduction or episodic non-adherence to treatment may select for the development of mutant viruses. Adherence to treatment is one of the key factors in avoiding development of resistance.

Patients should be advised to take Viracept every day as prescribed. Patients should not alter the

dose or discontinue therapy without consulting their physician. If a dose is missed, the patient should take the dose as soon as possible and then return to their normal schedule. However, if a dose is skipped, patients should not double the next dose.

Summary

Viracept, in combination with reverse transcriptase inhibitors, appears to have a low potential for resistance, which, coupled with its potent anti-retroviral activity, makes it an ideal candidate as a first-line protease inhibitor for use in combination regimens.

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6 Pharmacokinetics

Viracept (nelfinavir mesylate) has a three-times-daily dosing schedule, and is administered with food, making it very acceptable to patients. The convenient schedule reflects the pharmacokinetic profile of this rationally designed protease inhibitor. This chapter summarizes the key pharmacokinetic characteristics of Viracept.

Bioavailability and absorption

The pharmacokinetic properties of Viracept have been evaluated in healthy volunteers and HIV-infected patients. No substantial differences have been observed between healthy volunteers and HIV-infected individuals.

The oral bioavailability of Viracept compares well with that seen for other protease inhibitors. Studies in both humans and animals have shown that maximum plasma concentrations and the mean area under the curve (AUC) increases 2- to 3-fold when Viracept is given with food, compared with when given to fasting individuals.[1] In this respect, Viracept is similar to the protease inhibitors ritonavir and saquinavir, which are also given with food.[2] In contrast, indinavir must be taken on an empty stomach, as food reduces absorption by over 70%.[3]

After single and multiple doses of 500–750 mg (two or three 250 mg tablets) with food, peak nelfinavir plasma concentrations were typically achieved within 2–4 hours. After multiple doses of Viracept, 750 mg t.i.d. (steady state) for 28 days, peak plasma concentrations (C_{max}) averaged 3–4 µg/ml and plasma concentrations prior to the morning dose (trough) were 1–3 µg/ml (trough sample collection times averaged 11 hours after the previous evening dose). Under steady-state conditions with either 500 mg or 750 mg t.i.d., mean nelfinavir trough concentrations were approximately 25-fold greater than *in vitro* EC_{95} values.

Protein binding

Viracept is known to bind extensively to plasma proteins. *In vitro* assays using serum from both humans and rats showed ≤ 98% binding. A dynamic equilibrium exists between protein-bound Viracept, free Viracept and Viracept bound to HIV protease. The significance of such a high plasma protein-binding value is unclear, but similar patterns are seen with other protease inhibitors.[4]

In vitro studies examining this protein binding have been important in determining the most appropriate dose of Viracept for clinical use. Viracept has been found to bind extensively to isolated plasma proteins, namely alpha 1-acid glycoprotein (AAG) and human serum albumin. Because HIV-positive patients often have elevated serum levels of AAG, this has implications for the dose of Viracept used in clinical practice. In the presence of 0.9 mg/ml of AAG (the concentration determined for HIV-infected patients enrolled in phase I/II clinical trials), the estimated mean *in vitro* ED_{95} value for nelfinavir increased by 14-fold, to 500 nM. Throughout the dosing interval (with a dosage regimen of 500 mg t.i.d.), the plasma steady state concentration of nelfinavir would still be 2–6-fold greater than a conservative estimate of an *in vitro* ED_{95} value of 800 nM. While 500 mg t.i.d. would, in most instances, be effective in inhibiting HIV protease, the higher 750 mg t.i.d. dose would, in all circumstances, be expected to inhibit HIV protease completely.[4,5]

The terminal plasma elimination half-time for Viracept is typically between 3.5 and 5 hours, leading

to good maintenance of plasma concentrations above the ED_{95}.[6] Consistent with pharmacokinetic theory, the median trough concentration at the end of a 12-hour dose interval (750 mg b.i.d.) is lower than that for an 8-hour interval (500 mg t.i.d). This, together with the known absorption profile of Viracept, led to the selection of a three-times-daily dosing schedule in clinical studies to ensure consistent levels of nelfinavir that can inhibit HIV protease effectively and so markedly suppress HIV replication.[7]

Distribution

The distribution of Viracept in the body could have an marked effect on its activity. For example, preferential dispersal to the lymphatic tissue may increase its efficacy, as this is the main location for HIV replication. The apparent volume of distribution for Viracept in humans exceeds that of total body water, indicating extensive tissue penetration by Viracept.[8]

Results of studies in rats, examining the distribution of radiolabelled [^{14}C] Viracept,[8] have confirmed that tissue penetration of the drug is extensive. Viracept was detectable at higher levels in a number of tissues and organs, including the lymph nodes, compared with the plasma. The concentration of Viracept in the lymph nodes 4 hours after administration was 10 times higher than in plasma. These findings contrast with data collected during the preclinical study of the protease inhibitor indinavir, in which distribution to the lymph nodes was only 50%, compared with plasma.[9]

Although no studies have been conducted in humans, studies with a single 50 mg/kg dose of radiolabelled nelfinavir in rats showed that concentrations in the brain were lower than in other tissues, but exceeded the *in vitro* EC_{95} for antiviral activity. Other protease inhibitors – ritonavir, indinavir and saquinavir – also show limited penetration of the CNS in animal studies.[10] Studies into the extent of penetration and effects of Viracept in the CNS during clinical use are ongoing.

Distribution of Viracept across the placenta could prove important for the prevention of maternal–fetal transmission of HIV. Results of studies in rats indicate that placental transfer and lacteal secretion of Viracept can occur,[8,4] though this has still to be shown in humans. Indinavir is the only other protease inhibitor seen to cross the placenta in animals,[10] but this drug is associated with physiological hyperbilirubinaemia in adults, which could prove damaging to neonates. Hyperbilirubinaemia has not been associated with Viracept therapy. Viracept may therefore be more suited to the control of maternal transmission of HIV.[9]

Metabolism

Studies using radiolabelled [^{14}C] Viracept have revealed that 87% of Viracept administered is excreted *via* the faeces, with 78% excreted as oxidative metabolites. Only 1–2% of Viracept is excreted in the urine, indicating that the kidneys are a minor site for elimination.[11]

Hepatic oxidation is the major route by which Viracept is metabolized, though some glucuronidation products are also seen. Results of *in vitro* studies have shown that multiple cytochrome P450 (CYP) enzymes are involved.[11] Incubation with recombinant human enzymes and selective isoenzyme inhibitors has indicated that CYP3A4 is the major isoenzyme involved, accounting for around 50% of Viracept turnover.[11] Other cytochrome P450 isoforms involved in the metabolism of nelfinavir are CYP2C19/C9 and CYP2D6.

In vivo studies using inducers and inhibitors of CYP3A have confirmed its major role in Viracept metabolism.11 The concomitant use of a potent inducer of CYP3A (rifampin) decreased the mean steady-state plasma levels of Viracept by 82%. The more modest enzyme inducer rifabutin produced a 32% decrease. Potent inducers may reduce Viracept concentrations to below therapeutic levels. In contrast, a potent inhibitor of CYP3A – the antifungal ketoconazole – produced only a modest and clinically insignificant increase in plasma levels of Viracept. Thus, inhibitors of CYP3A, such as azole antifungals and macrolide antibiotics, are unlikely to interact adversely with Viracept.[11]

The oral bioavailability of Viracept compares favourably with that of other protease inhibitors

Viracept, 750 mg t.i.d., is the recommended regimen for maximum efficacy in a combined antiretroviral regimen

Viracept is metabolized mainly by the cytochrome P450 CYP3A4

Viracept administered at the recommended dosage results in nelfinavir trough levels significantly in excess of drug concentrations needed to suppress viral replication *in vitro*.

In vitro studies using human liver microsomes have shown that clinically relevant concentrations of Viracept are likely to inhibit only CYP3A and not other cytochrome P450 enzymes. The K_i value of 4.8 µM (2.7 µg/ml) is in the range of typical plasma Cmax values for Viracept (3–5 mg/ml) and is comparable to that seen for the protease inhibitor saquinavir. The protease inhibitors ritonavir and indinavir are both more potent inhibitors of CYP3A (about 7-fold lower K_i values). Viracept's K_i values for the other P450 enzymes were about 7-fold greater than the value for CYP3A, and therefore much higher than the Viracept concentrations seen in the plasma.[11]

The inhibition of CYP3A seen *in vitro* was investigated further *in vivo*. Administration of Viracept (750 mg t.i.d. for 7 days) had a marked effect on the kinetics of terfenadine, a substrate for CYP3A. In the absence of Viracept, administration of 60 mg of terfenadine resulted in no detectable plasma levels of terfenadine. During Viracept administration, however, the same dose of terfenadine resulted in a measurable plasma C_{max} for terfenadine (5.5 ng/ml to 15.3 ng/ml; median, 9.9 ng/ml). This indicates that Viracept, by competing for CYP3A, prevents the rapid metabolic breakdown of terfenadine.[12,13]

Administration of Viracept had a similar influence on saquinavir, leading to a 5-fold increase in saquinavir plasma concentrations. However, the protease inhibitor ritonavir produced a 20-fold increase in saquinavir levels, indicating that it is a more potent inhibitor of CYP3A activity than Viracept.[12,14]

Summary

The pharmacokinetic profile of Viracept has determined that a regimen of 750 mg t.i.d. administered with food is the most appropriate for use in clinical practice. There is some potential for drug interactions, as Viracept is metabolized by hepatic P450 enzymes, which are also responsible for inactivation of other medicines.

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7 Drug interactions

Viracept (nelfinavir mesylate) does not appear to interact unfavourably with other anti-HIV agents typically used in the management of HIV infection. Positive synergistic actions have been noted when Viracept is used in combination with saquinavir, suggesting that these two agents may have a role to play in disease management.

No clinically relevant Viracept pharmacokinetic changes occur during co-administration with nucleoside analogues

As described in the previous chapter, Viracept metabolism occurs mainly in the liver and is mediated by the hepatic cytochrome P450 enzyme system, mainly *via* the isoenzyme CYP3A. Interaction studies with Viracept have focused on drugs that are likely to be administered to patients with HIV disease (e.g. reverse transcriptase inhibitors [nucleoside analogues] and other protease inhibitors) and the potential for interactions with agents that are substrates, inhibitors or inducers of CYP3A. The results of these studies are summarized in Table 7.1.

Nucleoside analogues

Interactions between Viracept and the following nucleoside analogues have been investigated in HIV-positive patients:

- zidovudine plus lamivudine
- stavudine
- didanosine.

The results of these studies indicate that the pharmacokinetics of Viracept are unchanged by co-administration with these nucleoside analogues.[1] Viracept reduced the plasma area under the curve (AUC) and C_{max} for zidovudine (200 mg t.i.d.) by approximately 35%. This reduction is unlikely to be clinically significant, however, and is insufficient to require a dose adjustment. Increases in lamivudine plasma C_{max} and AUC were reported in a single-dose study in volunteers (Table 7.1),2 but were regarded as clinically insignificant in view of the good safety profile of lamivudine.[2]

This lack of pharmacokinetic interaction between Viracept and the nucleoside analogues is as expected from the distinct routes of metabolism and elimination for the two classes of antiretroviral agent. Viracept can thus be combined with nucleoside analogues without the need for dose-modifications of any agents.

Other protease inhibitors

Interactions between Viracept and other protease inhibitors have been studied rigorously,[1] because these agents are all metabolized by CYP3A. This suggests the potential for beneficial pharmacological interactions that could increase antiretroviral activity when protease inhibitors are given in combination. Studies have investigated the effect of a single dose of Viracept in the presence or absence of the following protease inhibitors, as well as the effect of a single dose of these protease inhibitors on a multidose regimen of Viracept (Table 7.2):

- saquinavir (soft-gelatin capsule formulation)
- indinavir
- ritonavir.

Saquinavir had no clinically significant effects on the plasma concentration of Viracept, whereas Viracept increased the plasma concentration of saquinavir by approximately 5-fold.[3] This effect reflects inhibition of metabolism of saquinavir by Viracept and is much less pronounced than the 20-fold increase in saquinavir plasma levels reported for the combination of ritonavir and saquinavir.[4] This is consistent with the results of *in vitro* stud-

Effects of Viracept on plasma AUC and C_{max} for co-administered drugs[2]

TABLE 7.1

Co-administered drug	Viracept dose	Healthy volunteers or patients	Co-admin. drug AUC	Co-admin. drug C_{max}
Lamivudine, 150 mg (single dose)	750 mg q8h x 7–10 days	Normal (n = 11)	↑10%	↑31%
Zidovudine, 200 mg (single dose)	750 mg q8h x 7–10 days	Normal (n = 11)	↓35%	↓31%
Stavudine, 30–40 mg b.i.d. x 56 days	750 mg t.i.d. x 56 days	Patients (n = 38)	↔	↔
Ethinyl oestradiol, 35 µg q.d. x 15 days	750 mg q8h x 7 days	Normal (n = 12)	↓47%	↓28%
Norethindrone, 0.4 mg q.d. x 15 days	750 mg q8h x 7 days	Normal (n = 12)	↓18%	↔
Terfenadine, 60 mg (single dose)	750 mg q8h x 7 days	Normal (n = 12)	↑(a)	↑(a)
Rifabutin, 300 mg q.d. x 8 days	750 mg q8h x 7–8 days	Normal (n = 10)	↑207%	↑146%
Saquinavir (soft gelatin capsules), 1200 mg (single dose)	750 mg t.i.d. x 4 days	Patients (n = 14)	↑392%	↑179%
Indinavir, 800 mg (single dose)	750 mg q8h x 7 days	Normal (n = 6)	↑51%	↔
Ritonavir, 500 mg (single dose)	750 mg q8h x 5 doses	Normal (n = 10)	↔	↔

(a) Terfenadine plasma concentrations were transiently measureable when co-administered with Viracept.

There is evidence of a synergistic, pharmacokinetic drug interaction between Viracept and saquinavir

Macrolide antibiotics and azole antifungal agents may interact with Viracept but dose modifications are not indicated

ies showing that Viracept is a much less potent inhibitor of CYP3A than ritonavir.[5]

Indinavir significantly increased the plasma concentration of Viracept and delayed elimination (Viracept AUC increased by 83%; elimination half-life increased by 22%) and *vice versa* (indinavir AUC increased by 51%; 5-fold increase in trough concentrations measured at 8 hours). These results suggest that dose reductions or a reduced frequency of dosing of both agents may be necessary if these two agents are given together.[1,5] There are currently no safety or efficacy data for Viracept in combination with Indinavir.

Ritonavir also significantly increased the plasma concentration of Viracept and delayed elimination (152% increase in AUC for Viracept; 156% increase in Viracept elimination half-life). A modest increase in the plasma concentration of ritonavir was observed (AUC increased by 8%).[1,5] There are currently no safety or efficacy data for Viracept in combination with ritonavir.

The results of these studies suggest that Viracept can be used in combination with other protease inhibitors. Dose reductions may be necessary when combining Viracept with indinavir or ritonavir. The safety and efficacy of Viracept plus saquinavir has been investigated in a phase II study (see Chapter 3).

Inhibitors of CYP3A

Agents that inhibit CYP3A are expected to increase the plasma concentration of Viracept and delay elimination. This is supported by results from a study of ketoconazole, a potent inhibitor of CYP3A.[5] Co-administration of ketoconazole and Viracept resulted in a 35% increase in the plasma AUC for Viracept. However, this increase was significantly less than that seen following co-administration of indinavir with ketoconazole, and does not necessitate dose reductions. The results of this study suggest that other selective inhibitors of CYP3A, such as the macrolide antibiotics and other azole antifungal agents, are unlikely to require dose reductions when co-administered with Viracept. This is in contrast to indinavir and ritonavir, both of which would require dose modification when used with some of these antimicrobial agents.[6,7]

Viracept interferes with the metabolism of terfenadine, probably *via* effects on CYP3A. A study in healthy volunteers found that co-administration of Viracept transiently increased plasma concentra-

TABLE 7.2

Doses investigated in pharmacokinetic interaction studies with protease inhibitors

Study	Viracept, single dose	Other protease inhibitor, multidose	Viracept multidose	Other protease inhibitor, single dose
AG1343-538	750 mg	Saquinavir (soft gelatin capsule), 1200 mg t.i.d. ∞ 4 days	750 mg t.i.d. ∞ 4 days	Saquinavir, 1200 mg
AG1343-529	750 mg	Indinavir, 800 mg every 8 hours ∞ 7 days	750 mg every 8 hours ∞ 7 days	Indinavir, 800 mg
AG1343-528	750 mg	Ritonavir, 500 mg every 12 hours ∞ 3 doses	750 mg every 8 hours ∞ 5 doses	Ritonavir, 500 mg

If coadministered with Viracept, rifabutin should be given at half the standard dose

tions of terfenadine to within detectable levels.[8] Viracept should thus not be administered concurrently with terfenadine because of the potential for cardiac arrhythmias.[6]

Inducers of CYP3A

Co-administration of agents that induce CYP3A would be expected to decrease plasma concentrations of Viracept and hence reduce efficacy.

A study of co-administration of Viracept and rifampicin found that the plasma AUC for Viracept was reduced by 82%.[9] This suggests that physicians should consider using an alternative prophylaxis against mycobacterium avium infection (MAI) during therapy with Viracept, or should discontinue Viracept therapy when rifampicin is required.[6,7]

Rifabutin has also been found to reduce plasma concentrations of Viracept when co-administered.[10] The AUC for Viracept decreased by 32%, accompanied by a 200% increase in rifabutin plasma AUC. Thus, a dose reduction of rifabutin to approximately half the standard dose is recommended when co-administered with Viracept.[6,7]

Oral contraceptives

The effects of Viracept on the pharmacokinetics of the components of oral contraceptives have been assessed in view of the importance of maintaining effective contraceptive control during antiretroviral therapy. The effects of a 7-day regimen of Viracept, 750 mg t.i.d., on a combination oral contraceptive that included 35 μg 17α-ethinyl oestradiol plus 0.4 mg norethindrone were assessed in healthy female volunteers.[11] A 47% decrease in ethinyl oestradiol and an 18% decrease in norethindrone plasma levels was observed. This suggests that alternative contraceptive measures should be considered during Viracept therapy.[6,12]

Other potential interactions

From the results of the drug-interaction studies described above, other potential drug interactions have been identified. Viracept should not be administered concurrently with astemizole and cisapride, because similar interactions to those seen with terfenadine are likely. The metabolism of potent sedatives, such as triazolam and midazolam, which are metabolized by CYP3A, may be inhibited by Viracept. These sedatives should not be co-administered with Viracept because of the risk of prolonged sedation. Plasma levels of calcium channel blockers may be elevated by concurrent administration with Viracept. Patients should thus be monitored for possible toxicity.[6]

Clinical significance

The results of extensive drug-interaction studies indicate that Viracept has no clinically significant

Viracept may alter the effectiveness of certain oral contraceptive agents

Viracept compares favourably with ritonavir and indinavir with regard to the potential for drug interactions

interactions with any of the nucleoside analogues tested (i.e. zidovudine, lamivudine, stavudine and didanosine), and hence can be combined with these agents without the need for dose modifications. Interactions with agents used in the treatment or prophylaxis of opportunistic infections (e.g. ketoconazole, other azole antifungal agents and macrolide antibiotics) are generally clinically insignificant and do not require dose modifications. Dose reduction is necessary for rifabutin during concurrent administration with Viracept, and co-administration of rifampicin is not recommended.

In terms of potential for drug interactions, Viracept compares favourably to ritonavir and indinavir, both of which are more potent inhibitors of CYP3A. Ritonavir also inhibits other isoenzymes of cytochrome P450 and is thus subject to many more serious drug interactions than have been reported for Viracept. Indinavir is also associated with drug interactions necessitating dose modification (e.g. ketoconazole).

Viracept interacts synergistically with saquinavir to increase plasma levels of saquinavir. The therapeutic benefit of this combination is being assessed.

Summary

Close investigations have found that there are few unfavourable interactions between Viracept and drugs generally used in the management of HIV infection.

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11. F. Hoffmann-La Roche Ltd., Basle, Switzerland / Agouron Pharmaceuticals Inc., La Jolla, USA. Data on file: Viracept (nelfinavir mesylate); Study AG1343-526.

12. F. Hoffmann-La Roche Ltd., Basle, Switzerland / Agouron Pharmaceuticals Inc., La Jolla, USA. Data on file: Viracept (nelfinavir mesylate); AMA vol 8 p42, 43.

8 Administration and formulation

Viracept is available in two formulations: Viracept Tablets and Viracept Oral Powder. The tablet formulation is recommended for adults and older children, while the powder formulation is recommended for children unable to take the tablets.

Viracept Tablets

Viracept Tablets contain 292.25 mg of nelfinavir mesylate, which corresponds to 250 mg of nelfinavir (as the free base). Tablets also contain calcium silicate, crospovidone, magnesium stearate, indigo carmine (E132) as powder and aluminium lake.

Tablets are administered orally and should be ingested with food. The recommended dose for patients aged 13 years and older is 750 mg (i.e. three 250 mg tablets), taken three times a day by mouth. For children aged 13 years and younger, the recommended dose is 20–30 mg/kg body weight per dose, given three times a day. The recommended number of tablets to be administered three times a day for paediatric patients is thus:

- body weight, 18–<23 kg: 2 tablets
- body weight, ≥ 23 kg: 3 tablets.

Viracept Tablets have a shelf life of 18 months. Storage in the original container at room temperature (15–30°C) is recommended.

Viracept Oral Powder

Viracept Oral Powder contains 58.45 mg of nelfinavir mesylate, corresponding to 50 mg of nelfinavir (as free base). Viracept Oral Powder (50 mg/g) is an off-white powder containing 50 mg of nelfinavir free base in each level scoopful (1 g). The Oral Powder also contains microcrystalline cellulose, maltodextrin, dibasic potassium phosphate, crospovidone, hydroxypropyl methyl cellulose, aspartame (E951) sucrose palmitate, and natural and artificial flavour.

TABLE 8.1

Body weight (kg)	Number of level 1g scoops	Corresponding nelfinavir content (mg)	Number of level teaspoons
7.5 to < 8.5	4	200	1
8.5 to < 10.5	5	250	1 1/4
10.5 to < 12	6	300	1 1/2
12 to < 14	7	350	1 3/4
14 to < 16	8	400	2
16 to < 18	9	450	2 1/4
18 to < 23	10	500	2 1/2
≥ 23	15	750	3 3/4

(source, package insert p1, new IB p2.2)

Recommded paediatric dose of Viracept Oral Powder. Viracept Oral Powder contains 50 mg nelfinavir as free base in each level scoopful (1g).

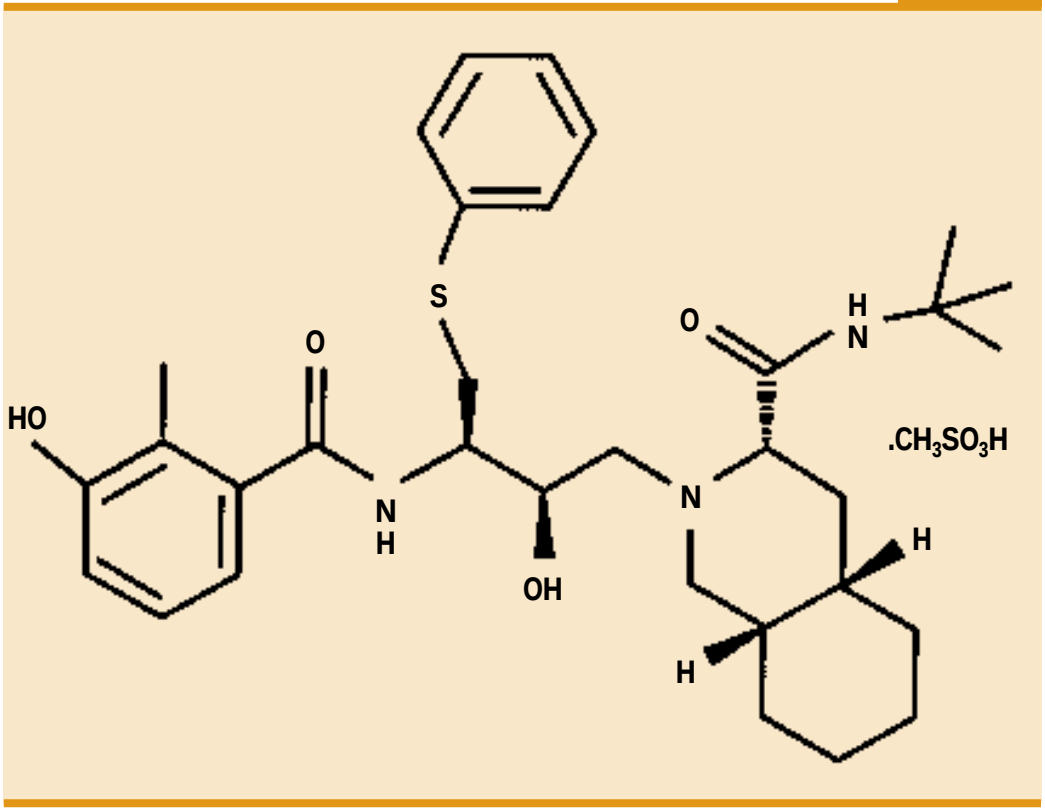
Viracept Oral Powder should be ingested with food and may be mixed with water, formula milk, soya milk, dietary supplements or puddings. Viracept Oral Powder should not be mixed with acidic media such as acidic food or juices (e.g. orange juice, apple juice or apple sauce). Once mixed with the medium, Viracept Oral Powder should be used within 6 hours. The recommended dose for children aged 13 years or younger is 20–30 mg/kg body weight per dose given three times a day. For older children or adults unable to take tablets, the recommended dose of Viracept Oral Powder is 750 mg three times a day (t.i.d.). The recommended paediatric dose of Viracept Oral Powder according to body weight is shown in Table 8.1.

9 Chemical characteristics

The active ingredient of Viracept is nelfinavir mesylate. This is a non-peptidic inhibitor of the HIV-1 protease. The chemical structure of nelfinavir, its molecular formula and chemical name are shown in Figure 9.1.

Nelfinavir mesylate has a molecular weight of 663.90 and is a white to light brown amorphous powder. Nelfinavir mesylate is slightly soluble in water, soluble in ethanol and isopropanol, and is freely soluble in methanol.

FIGURE 9.1



Chemical structure, chemical name and molecular formula of nelfinavir mesylate.

10 Summary of product characteristics

Compound:	Nelfinavir mesylate
Molecular formula:	$C_{32}H_{45}N_3O_4S$. CH_4O_3S[1]
Molecular weight:	663.90 (567.79 as free base)
Chemical name:	[3S-[2(2S*,3S*),3α,4αβ,8αβ]]-*N*-(1,1-dimethylethyl) decahydro-2-[2-hydroxy-3-[(3-hydroxy-2-methylbenzoyl)amino] -4-(phenylthio)butyl]-3-isoquinolinecarboxamide mono-methanesulfonate (salt)
Name of pharmaceutical product:	Viracept
Pharmaceutical form:	Tablet, Oral Powder

Qualitative and quantitative composition

Viracept Tablets contain 292.25 mg of nelfinavir mesylate per tablet, corresponding to 250 mg of nelfinavir (as free base).

Viracept Oral Powder contains 58.45 mg of nelfinavir mesylate per gram, corresponding to 50 mg of nelfinavir (as free base).

Therapeutic indications

Viracept is indicated in combination with antiretroviral nucleoside analogues for the treatment of HIV-1-infected patients with advanced or progressive immunodeficiency.

Posology and method of administration

Viracept tablets are administered orally and should (preferably) be ingested with food.

Viracept Oral Powder should (preferably) be ingested with food.

Patients aged 13 years and older

Viracept Tablets are recommended. The recommended dosage of Viracept Tablets is 750 mg (3 x 250 mg tablets) three times a day (t.i.d.) by mouth. For patients unable to take tablets, the recommended dose of Viracept Oral Powder is 750 mg t.i.d.

Children aged 13 years and younger

For children, the recommended dose is 20–30 mg/kg body weight per dose given t.i.d. Either Tablets or Oral Powder may be administered.

Paediatric dose

The recommended dose of Oral Powder to be administered t.i.d. is given in Table 8.1. Oral Powder may be mixed with water, formula milk, soya milk, dietary supplements or puddings. It is recommended that Oral Powder mixed with media be used within 6 hours. Dosing media not recommended include any acidic food or juice (e.g. orange juice, apple juice, apple sauce). Do not add water to bottles of Oral Powder.

Viracept Tablets may also be administered t.i.d. to paediatric patients with body weight 18 kg or greater (18 to <23 kg, 2 tablets; ≥ 23 kg, 3 tablets).

Contraindications

Hypersensitivity to nelfinavir or any of the excipients.

Viracept is contraindicated in breast-feeding women.

Viracept should not be administered concurrently with drugs that have narrow therapeutic windows and that are substrates of CYP3A4. Co-administra-

tion may result in competitive inhibition of the metabolism of these drugs and create the potential for serious and/or life-threatening adverse events, such as cardiac arrhythmias (e.g. terfenadine, astemizole, cisapride), prolonged sedation or respiratory depression (e.g. triazolam, midazolam).
Viracept must not be given with rifampicin. Rifampicin decreases nelfinavir plasma AUC by 82%.

Special warnings and special precautions for use

Caution should be taken when administering Viracept to patients with impaired renal and hepatic function.
The safety and activity of nelfinavir in children below the age of 2 years has not been established. Therefore, nelfinavir should only be used in children below the age of 2 years only when the potential benefits clearly outweigh the risks.
Caution is advised whenever Viracept is co-administered with drugs that are inducers or inhibitors and/or substrates of CYP3A4; such combinations may require dose adjustment.
Haemophiliac patients should be made aware that there have been reports of increased bleeding, including spontaneous skin haematomas and haemarthroses, with protease inhibitor administration.

Use during pregnancy and lactation

No treatment-related adverse events were seen in animal reproductive toxicity studies in rats at doses providing systemic exposure comparable to that observed with the clinical dose. Clinical experience in pregnant women is lacking. Until additional data become available, Viracept should be given in pregnancy only after special consideration.

Health experts recommend that HIV-infected women must not breast-feed their infants under any circumstances in order to avoid transmission of HIV. Studies in lactating rats showed that nelfinavir is excreted in breast milk. There are no data available on nelfinavir excretion into human breast milk. Until more data become available, mothers must be instructed to discontinue breast-feeding if they are receiving Viracept.

Undesirable effects

The majority of adverse events were of mild intensity. The most frequently reported adverse event among patients receiving Viracept was mild to moderate diarrhoea. Detailed descriptions can be found in Chapter 4.

Pharmaceutical particulars

List of excipients

Tablets: calcium silicate, crospovidone, magnesium stearate, indigo carmine (E132), as powder and aluminium lake.
Oral Powder: microcrystalline cellulose, maltodextrin, dibasic potassium phosphate, crospovidone, hydroxypropyl methylcellulose, aspartame (E951), sucrose palmitate, natural and artificial flavour.

Shelf-life

Viracept Tablets - 18 months
Viracept Oral Powder - 12 months

Storage

Store in the original container at 15–30°C

Nature and contents of container
Viracept Tablets are provided in plastic bottles containing 270 tablets.
Viracept Oral Powder is provided in plastic bottles containing 144 grams of Oral Powder with a 1 gram scoop.

References

1. Viracept™ tablets 250 mg/oral powder 50 mg/g (Nelfinavir™). Summary of product characteristics. Opinion Documents English. EMEA, November 1997.

VIRACEPT®

nelfinavir

Power you can live with

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