Drugs of the Future 1998, 23(2): 133-141

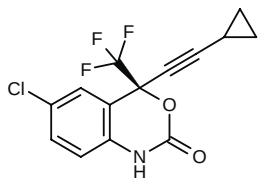
Efavirenz

Prop INN

Antiviral for AIDS
Reverse Transcriptase Inhibitor

L-743726
DMP-266
Sustiva™

(*S*)-(–)-6-Chloro-4-(cyclopropylethynyl)-4-(trifluoromethyl)-2,4-dihydro-1*H*-3,1-benzoxazin-2-one



$C_{14}H_9Cl_3NO_2$ Mol wt: 315.68

CAS: 154598-52-4

EN: 207217

Synthesis

Efavirenz has been obtained by two related ways: Scheme 1.

1) The acylation of 4-chloroaniline (I) with pivaloyl chloride (II) by means of Na_2CO_3 in toluene gives the expected anilide (III), which is acylated with ethyl trifluoroacetate by means of butyl lithium in THF yielding, after hydrolysis with HCl, 2'-amino-5'-chloro-2,2,2-trifluoroacetophenone (IV). The benzylation of (IV) with 4-methoxybenzyl chloride (V) in basic alumina affords the protected acetophenone (VI), which is regioselectively condensed with cyclopropylacetylene (VII) [obtained by cyclization of 5-chloro-1-pentyne (VIII) by means of butyl lithium in cyclohexane] by means of butyl lithium in THF in the presence of (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidinyl)-1-propanol (IX) giving the (*S*)-isomer of the tertiary alcohol (X) exclusively. The cyclization of (X) with phosgene and triethylamine or K_2CO_3 in toluene/THF yields the benzoxazinone (XI), which is finally deprotected with ceric ammonium nitrate in acetonitrile/water (1-3).

2) The condensation of 2'-amino-5'-chloro-2,2,2-trifluoroacetophenone (IV) with cyclopropylacetylene (VIII) by means of butyl lithium or ethylmagnesium bromide in THF gives (±)-2-(2-amino-5-chlorophenyl)-4-cyclopropyl-1,1,1-trifluoro-3-butyn-2-ol (XII). The cyclization of (XII) with carbonyldiimidazole (XIII) in hot THF yields the racemic benzoxazinone (XIV). Compound (XIV) is submitted to optical resolution by condensation with (*S*)-(–)-camphanoyl chloride by means of dimethylaminopyridine (DMAP) in dichloromethane to give the acyl derivative (XVI) as a diastereomeric mixture that is resolved by crystallization and finally decomposed with HCl in ethanol or butanol (4-6).

Description

White crystals, m.p. 131-2 °C, $[\alpha]_D^{20}$ –84.7° (c 0.005, $CHCl_3$) (4, 5).

Introduction

Since the discovery in 1981 of HIV, the virus causing AIDS, the development of drugs to treat HIV infection has been a priority. One of the principal targets for inhibition of HIV has been the blockade of the various enzymes which play a critical role in the life cycle of the virus, such as protease and reverse transcriptase. Protease inhibitors are discussed in a separate monograph in this issue.

Several HIV reverse transcriptase inhibitors have been developed, and some of them have reached the market. These inhibitors generally fall into two structural classes: nucleoside analogs (*e.g.*, zidovudine) and non-nucleosides (*e.g.*, nevirapine).

The first reverse transcriptase inhibitor to reach the market was the nucleoside analog zidovudine (Glaxo Wellcome's Retrovir®), which was launched in 1987. The first reports of treatment with zidovudine were very promising, although its benefits could not be sustained in many patients due to the emergence of viral resistance. In an effort to delay the emergence of viral resistance and improve clinical outcome, the first nucleoside analog combination therapies were studied. Extremely positive results were obtained in trials such as ACTG 175, which began in 1991 and evaluated the combination of zidovudine with didanosine or zalcitabine, and the European Australian Delta study, which began in 1992 and evaluat-

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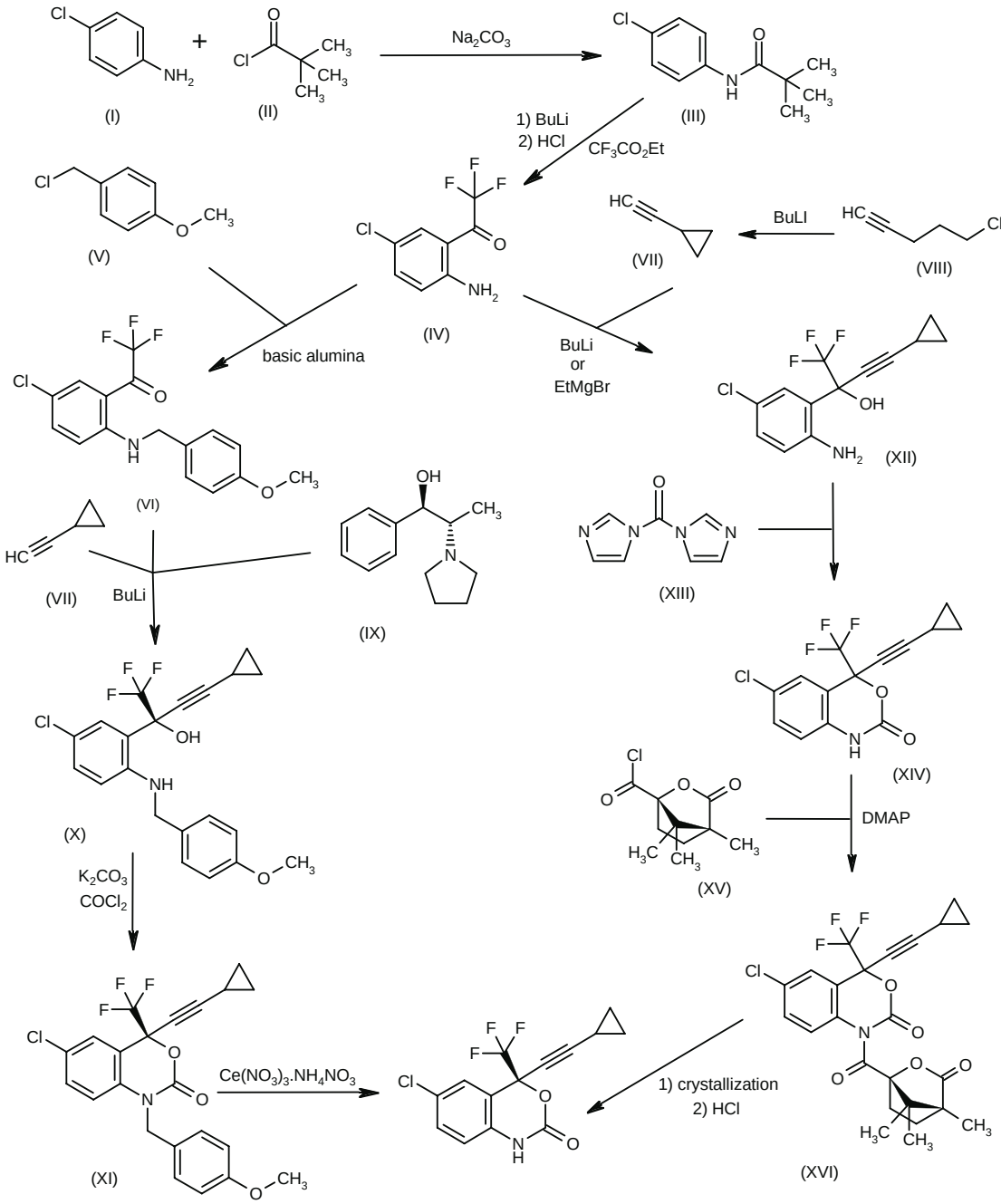
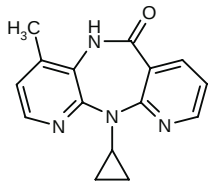
Scheme 1: Synthesis of Efavirenz



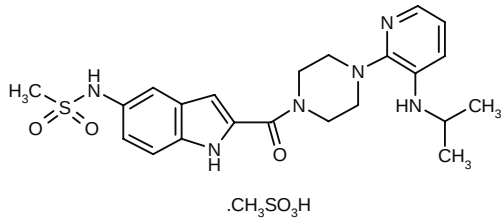
ed the same drug combinations. The CAESAR study (1995) compared the efficacy of adding lamivudine (3TC), lamivudine + loviride or placebo to zidovudine-containing anti-HIV regimens. This study demonstrated the efficacy of adding lamivudine to zidovudine in terms of slowing disease progression and improving survival.

The results of these and other combination therapy studies brought the era of zidovudine monotherapy to a close. Currently, the guiding principle for treating HIV-infected patients is to initiate treatment with two nucleoside analogs plus a highly potent protease inhibitor, and to modify treatment in case of treatment failure, adverse effects, poor compliance, potential drug interactions or use of a suboptimal regimen (7).

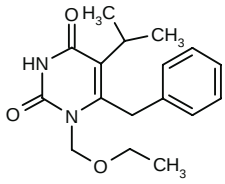
Table I: Nonnucleoside reverse transcriptase inhibitors launched (year) and in development.



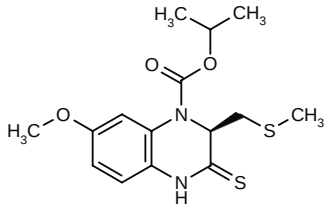
Nevirapine
(1996)



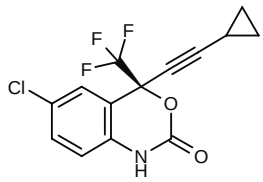
Delavirdine mesilate
(1997)



MKC-442



Talviraline



Efavirenz

Two nonnucleoside reverse transcriptase inhibitors have been launched to date: nevirapine (Viramune®; Boehringer Ingelheim) and delavirdine mesilate (Rescriptor®; Pharmacia & Upjohn). Others are in development, according to the Prous Science databases, including MKC-442 (Mitsubishi Chem.) and talviraline (Bayer/Hoechst Marion Roussel) (Table I). In the continuing quest for improved anti-HIV drugs, scientists at DuPont Merck synthesized a novel series of benzoxazinone compounds with reverse trancriptase inhibitory activity and selected the most potent compound in this group, DMP-266 (efavirenz), for further development.

Pharmacological Actions

DMP-266 (efavirenz) was discovered as part of a project to develop new nonnucleoside reverse transcriptase inhibitors (NNRTIs) with potent antiviral activity, including against resistant strains, and a better pharmacokinetic profile than that exhibited by preceding compounds of this class. The anti-HIV activity of efavirenz was established *in vitro* against wild-type HIV reverse transcriptase (K_i = 2.93 nM). It inhibited HIV-1 replicative viral spread in cell culture with a 95% inhibitory concentration of 1.5 nM, and maintained this level of activity against a panel of NNRTI-resistant mutant viruses, each expressing a single RT amino acid substitution (IC_{95} = ≤ 1.5 μM) (6, 8).

The rapid development of resistance to prior RTIs has been seen in the past due to such single amino acid substitutions. With efavirenz, in contrast, resistance was shown to develop less slowly. As seen by yield reduction assays in MT-2 cells, resistance increased by 1-, 7-, 11- and 24-fold following 0, 12, 15 and 24 serial passages, respectively (9).

The central nervous system often serves as a safe haven for the HIV virus, as many anti-HIV drugs are unable to cross the blood-brain barrier (BBB). Thus, a long-term study was conducted in cynomolgus monkeys administered efavirenz for 57 weeks. The compound was administered to 3 groups of monkeys at doses of 15, 45 or 75 mg/kg for the first week, then twice daily for the next 56 weeks. Plasma and cerebrospinal fluid (CSF) concentrations of efavirenz were measured after 57 weeks of treatment, with samples taken either 3 or 16 h postdosing. At clinically relevant plasma levels, efavirenz was found to readily cross the BBB and to reach CSF levels at or above the IC90s for most wild-type and clinical strains of HIV-1, including those with K103N mutations, the most frequently observed mutation in patients whose viral loads rebound after treatment with efavirenz (10).

Pharmacokinetics and Metabolism

The pharmacokinetics of efavirenz were evaluated in rats and rhesus monkeys. Drug clearance was rapid in rats, but not in monkeys, following i.v. dosing. The volume of distribution was large in both species, representing 2-4 times the body water volume and reflecting the extensive tissue binding of the compound; the half-life in monkeys was longer than 2.5 h at the dose of 1.0 mg/kg i.v. Bioavailability in rats was 16% at a dose of 10 mg/kg and in monkeys was 42% at the dose of 2 mg/kg. Administration to monkeys of a 2-mg/kg oral suspension produced peak drug levels of 0.5 μM at ~ 3 h and a 10-mg/kg oral dose produced peak plasma levels of 3.22 μM (6).

In bile duct-cannulated rats given [^{14}C]-labeled efavirenz (5 mg/kg i.v.), more than 99% of the radioactivity administered was excreted in bile and the remainder (< 0.5%) in the urine. Data obtained on blood clearance and excretion indicated that efavirenz undergoes a high hepatic first-pass effect (11).

CLP, Vd_{ss} and $t_{1/2}$ values obtained in fasted monkeys receiving a dose of 1 mg/kg i.v. were 11.6 ml/min/kg, 2.4 l/kg and 158 min, respectively, while blood clearance was 15.2 ml/min/kg. Urinary and fecal excretion of efavirenz were approximately 50% and 32%, respectively, both at 5 mg/kg i.v. and at 10 mg/kg p.o., reflecting the good oral absorption of the compound. C_{max}, t_{max} and bioavailability values were 0.5 μM, 176 min and 42%, respectively, in monkeys at the dose of 2 mg/kg p.o.; at higher doses (10, 40 or 80 mg/kg), AUC increased in a fashion that was more than dose-proportional. In all cases, plasma concentrations increased rapidly and then plateaued, remaining high for 4-20 h, and the plasma concentration-time curve indicated that absorption of the compound was prolonged at these doses. Higher doses (120 or 160 mg/kg) of efavirenz were not tolerated well by these monkeys, most of whom suffered nausea and vomiting due to the delayed gastric emptying of the compound (11).

The steady-state plasma levels of efavirenz were determined in humans in a clinical pharmacokinetics study. Following administration at doses of 200, 400 or 600 mg p.o., mean steady-state plasma levels were 2.00, 4.34 and 4.45 μM, respectively. Based on 8-h trough levels, these plasma levels were high enough (1.9-4.62 μM) to inhibit the replication of wild-type and mutant HIV-1 strains, including K103N mutant viruses, after once-daily administration at the doses above (12).

A double-blind clinical study was designed to evaluate the pharmacokinetics of efavirenz, administered alone or in combination with indinavir, in 16 HIV-infected patients with CD4 counts in the range of 200-500 and HIV RNA of > 20,000 copies/ml. Patients were randomized to treatment with efavirenz (200 mg q.d.) or placebo for 2 weeks, after which time indinavir (800 mg q8h) was added to the treatment regimen for all patients. The area under the indinavir plasma concentration-time curve (AUC) was 37% lower in patients also administered efavirenz as compared to those in the placebo group (mean indinavir AUC = 17 μM.h *vs.* 27 μM.h, respectively). Efavirenz pharmacokinetic parameters were not significantly affected by the addition of indinavir (13).

In another study the pharmacokinetic interactions of efavirenz and indinavir were evaluated following slightly different dosing regimens. Groups I and II received efavirenz or placebo monotherapy, respectively, for 2 weeks, followed by the addition of indinavir for 12 weeks. Group III received indinavir monotherapy for 2 weeks, followed by the addition of efavirenz or placebo for 12 weeks. Steady-state plasma concentrations of efavirenz were reached in groups I and II within 2 weeks, and the subsequent addition of indinavir did not affect efavirenz pharmacokinetics. Indinavir plasma concentrations in group III also reached steady state within 2 weeks, but the addition of efavirenz caused the indinavir $AUC_{(0-8)}$ to decrease by approximately 35%. This effect was tentatively attributed to efavirenz-mediated induction of the 3A4 isoform of P450 and could be offset by increasing the dosage of indinavir (14).

The pharmacokinetic interaction of efavirenz with nelfinavir mesylate has been explored in a single study in 18 healthy volunteers. Eight subjects were administered nelfinavir (750 mg q8h) for 7 days, to which efavirenz (400 mg q.d.) was added for a further 7 days. In the other treatment arm, 10 subjects received efavirenz (400 mg q.d.) for 7 days, with the addition of nelfinavir (750 mg q8h) during the next 7 days. No significant differences in pharmacokinetic parameters were observed between the two treatment arms on day 14. The nelfinavir AUC increased by approximately 15% with the addition of efavirenz, perhaps due to the induction of P450 by efavirenz. Based on the pharmacokinetic data obtained in this study, further trials evaluating the combination were reported to be in progress (15, 16).

Human studies have also been conducted evaluating the pharmacokinetic interactions of efavirenz with other protease inhibitors including 141W94 (amprenavir; Vertex/Glaxo Wellcome/Kissei) (17), with the macrolide antibiotics azithromycin and clarithromycin (18) and with ethinyl estradiol in females (19).

Clinical Studies

In the same double-blind pilot study reported above (13), the efficacy and safety of efavirenz were also assessed. After 2 weeks of efavirenz monotherapy, mean CD4 counts had increased by 96 ± 63 cells/mm^3 and HIV RNA had decreased by 98%; these parameters did not change significantly from baseline in placebo-treated patients. After 12 weeks of combination therapy, HIV RNA decreased by > 99%. In 6/11 patients on efavirenz + indinavir and 1/5 on indinavir + placebo, HIV RNA levels were below 400 copies/ml. CD4 counts increased by > 100 cells in both treatment arms (13) (Box 1).

Another study enrolled 16 patients with CD4 counts of 100-500 cells and > 20,000 copies of HIV RNA, who were treated first with DMP-266 monotherapy (200 mg once daily) or placebo for 2 weeks, followed by addition of indinavir (1000 mg every 8 h) for 12 weeks. Of those on combination therapy, 45% showed decreases in HIV RNA levels to below 400 copies/ml compared to 20% of patients on indinavir alone. Mean increases in CD4 counts of > 100 cells were observed in both groups. Generally good tolerance was reported (20) (Box 2).

In a multicenter, double-blind, placebo-controlled phase II trial in 137 antiretroviral-naive HIV-infected patients randomized to treatment with efavirenz (200, 400 or 600 mg once daily) + zidovudine (ZDV; 300 mg b.i.d.) + lamivudine (3TC; 150 mg t.i.d.) or placebo for 24 weeks, all 21 patients receiving the highest dose of efavirenz achieved HIV RNA levels below the level of quantification. The most frequent side effects were nausea, headache and fatigue (21, 22) (Box 3).

Box 1: Efficacy and tolerability of efavirenz alone or in combination with indinavir (13).

Design	Double-blind clinical trial		
Population	HIV-positive patients with CD4 counts of 200-500 and >20,000 HIV RNA copies/ml (n = 16)		
Treatments	Efavirenz, 200 mg 1x/day x 2 weeks → id. + indinavir, 800 mg t.i.d. Placebo x 2 weeks → id. + indinavir, 800 mg t.i.d.		
Results		at 2 weeks (monotherapy)	at 12 weeks (combination therapy)
	Reduction in HIV-RNA	E+I (-3.2 $\log_{10}$) > P+I	
	Increase in CD4 count	E+I (63 cells/mm^3) > P+I	
	Improvement rate, HIV RNA[1]		E+I (55%) > P+I (20%)
Conclusions	Efavirenz adds significant efficacy to a treatment with indinavir alone		

[1]Less than 400 RNA copies/ml. Source: Prous Science CTLine database.

Box 2: Efficacy and tolerability of efavirenz alone or in combination with indinavir (20).

Design	Double-blind clinical trial		
Population	HIV-positive patients with CD4 counts of 200-500 and >20,000 HIV RNA copies/ml (n = 16)		
Treatments	Efavirenz, 200 mg 1x/day x 2 weeks → id. + indinavir, 1000 mg t.i.d. Placebo x 2 weeks → id. + indinavir, 1000 mg t.i.d.		
Results		at 2 weeks (monotherapy)	at 12 weeks (combination therapy)
	Reduction in HIV-RNA	E+I (-1.6 $\log_{10}$) > P+I	
	Increase in CD4 count	E+I (92 cells/mm^3) > P+I	
	Improvement rate, HIV RNA[1]		E+I (45%) > P+I (20%)
Conclusions	Efavirenz adds significant efficacy to a treatment with indinavir alone with no increase in toxicity		

[1]Less than 400 RNA copies/ml. Source: Prous Science CTLine database.

A long-term (60 weeks) trial in 101 asymptomatic or mildly symptomatic patients compared the safety, tolerability and antiretroviral activity of efavirenz (200 mg/day, increasing to 600 mg/day after at least 36 weeks) in combination with indinavir (800 or 1000 mg t.i.d.) to indinavir alone. Those on indinavir alone had stavudine (d4T) and efavirenz added at 12 weeks. After 60 weeks of treatment, 91% and 79% of those on efavirenz + indinavir and efavirenz + d4T + indinavir, respectively, had HIV RNA below quantifiable levels (< 400 copies/ml), and all of those showing unquantifiable levels at this time on efavirenz + indinavir had undetectable levels (< 1 copy/ml) at 24 weeks. A greater increase in $CD4^+$ cells was observed on efavirenz + indinavir compared to triple therapy. Treatment was generally well tolerated in both groups. The study also showed that patients who achieved undetectable levels had significantly better long-term results, as measured by viral load rebound,

Box 3: Efficacy and safety of efavirenz plus zidovudine plus lamivudine in HIV-positive patients (21, 22).

Design	Multicenter, double-blind, placebo-controlled clinical trial
Population	Antiretroviral-naive HIV-positive patients (n = 137)
Treatments	Efavirenz, 200-600 mg/day + zidovudine + lamivudine x 16 weeks (n = 103) Placebo (n = 34)
Adverse events	E+Z+L, 93% (nausea in 59%, headache in 35%, fatigue in 47%)
Conclusions	Efavirenz added to a combination of zidovudine and lamivudine may represent a simple, initial treatment in antiretroviral-naive, asymptomatic patients to save protease inhibitors for second-line therapy

[1]Less than 400 RNA copies/ml. Source: Prous Science CTLine database.

Box 4: Effect of indinavir alone or in combination with efavirenz on the viral load in HIV-positive patients (23).

Design	Randomized clinical trial			
Population	HIV-positive patients with a CD4 count of 283.6 ± 118.2 cells/mm^3 (n = 101)			
Treatments	Efavirenz (200-600 mg p.o. 1x/day) + indinavir (800-1000 mg p.o. t.i.d.) (n = 59) Indinavir (800-1000 mg p.o. t.i.d.)[1] (n = 42)			
Results	Viral load (HIV RNA)	12 weeks	16 weeks	24 weeks
	< 1 copies/ml	E+I (64%) > I (32%)	E+I (71%) > I (38%)	E+I (88%) > I (62%)
	< 400 copies/ml	E+I (74%) > I (50%)	E+I (87%) > I (56%)	E+I (94%) > I (74%)
Conclusions	Efavirenz combined with indivanir can suppress HIV RNA to undetectable levels in more patients than indinavir in monotherapy			

[1]After 12 weeks, patients on indinavir monotherapy could add efavirenz and stavudine. Source: Prous Science CTLine database.

Box 5: Safety, tolerability and efficacy of efavirenz plus indinavir in asymptomatic or mildly symptomatic patients (24).

Design	Multicenter, randomized, comparative clinical trial
Population	HIV-positive patients with no or mild symptoms (n = 101)
Treatments	Efavirenz, 200 mg/day + indinavir, 800-1000 mg t.i.d.[1] Efavirenz, 200 mg/day + stavudine + indinavir, 800-1000 mg t.i.d.[1]
Results	Improvement rate, HIV-RNA[2], E+I (91%) > E+S+I (79%) CD4 count increase, E+I (267) > E+S+I (210) ($p < 0.05$)
Conclusions	Efavirenz adds significant activity to indinavir to indinavir with no decrease in tolerability

[1]Fifty-nine patients initiated treatment with both drugs; 42 patients initiated treatment with indinavir alone and efavirenz and stavudine were added after 12 weeks. After at least 36 weeks of therapy, doses of efavirenz were increased to 600 mg/day. [2]Less than 400 RNA copies/ml. Source: Prous Science CTLine database.

than those only achieving unquantifiable levels (23, 24) (Boxes 4, 5). Furthermore, the investigators stated that, based on the good anti-HIV activity and tolerability of once-daily efavirenz, this compound represents a valuable addition to combination therapy and may improve patient adherence to a prescribed regimen (25) (Box 6).

The relative risk of treatment failure on efavirenz/indinavir combinations was found to be linearly related to residual detectable viral load, baseline plasma HIV RNA and age of the patient. The time to treatment failure was significantly shorter in those patients with detectable virus than those with undetectable viral load (82% *vs.* 25% within 100 days of nadir). Thus, the replication of residual virus may be biologically significant, and it appears that the achievement of maximal viral suppression should be the goal of antiretroviral therapywith efavirenz and other anti-HIV drugs (26).

Box 6: Safety and efficacy of efavirenz in combination with indinavir (25).

Design	Multicenter clinical trial
Population	HIV-1-positive patients with 5.06 $\log_{10}$ HIV-1 RNA copies (n = 101)
Treatments	Efavirenz (200 mg q.d.) + indinavir (800-1000 mg t.i.d.) x 24 weeks Indinavir (800-1000 mg t.i.d.) x 24 weeks
Withdrawals	82% of patients completed the trial
Tolerability	Both treatments were well tolerated
Results	Decrease in HIV-1 RNA levels, E+I (4.75 $\log_{10}$) > I (2.53 $\log_{10}$) ($p < 0.05$) Improvement rate[1] at week 24, E+I (94%) > I (47%) Increase in CD4 cells, E+I (199) > I (108) ($p < 0.05$)
Conclusions	Efavirenz once daily added to indinavir increases the antiviral activity with no loss in tolerability

[1]Patients with undetectable (< 400 copies/ml) RNA levels. Source: Prous Science CTLine database.

Box 7: Potential for development of resistance to efavirenz (27).

Design	Open clinical trial
Population	HIV-positive patients with rebound in viral load after combination therapy with efavirenz and indinavir
Treatments	Efavirenz → efavirenz + indinavir[1] Indinavir → efavirenz + indinavir[1] No treatment → efavirenz + indinavir[1] Efavirenz → placebo + indinavir[1] Indinavir → placebo + indinavir[1] No treatment → placebo + indinavir[1]
Results	Patients with significant rebounds in viral load, E → P+I 6/10 (60%) > E → E+I, 11/21 (52.4%) > P+I 13/34 (38.2%) ≈ I→P+I 6/17 (35.3%) > I→E+I 3/18 (16.7%) > E+I 10/92 (10.9%)
Conclusions	Monotherapy with efavirenz is rapidly associated with resistance and subsequent treatment failure; however, efavirenz enhances the antiviral activity of indinavir when used in combination

[1]Initial monotherapy lasted for 14 days. Doses were: efavirenz, 200 mg q.d.; indinavir, 800-1200 mg t.i.d. Source: Prous Science CTLine database.

Resistance Studies

The clinical promise of the nonnucleoside reverse transcriptase inhibitors has, for the most part, remained unfulfilled. This is primarily due to the rapid emergence of viral variants in HIV-infected individuals (6). Consequently, several resistance studies have been conducted with efavirenz, and the drug has been evaluated in various combinations. In particular, several studies have been performed to evaluate the combination of efavirenz with indinavir.

The K103N viral mutation was found to occur with surprising frequency in a study assessing the combination of indinavir + efavirenz. In this study, patients treated for as little as 2 weeks with efavirenz monotherapy (200 mg/day) prior to the addition of indinavir were found to suffer viral mutations contributing to later rebounds of viral load and subsequent treatment failure on combination therapy. Therefore, the investigators stressed that efavirenz should not be used as monotherapy, even for short periods (27) (Box 7).

A different conclusion was reached by the investigators in two other studies, however. *In vitro* studies indicated that the resistance profile of efavirenz partially overlaps that of other NNRTIs such as delavirdine and nevirapine, although the compound retains good potency against a number of NNRTI-resistant mutants (*e.g.*, variants carrying Y181C and V106A mutations). The mutation most frequently observed in cases of viral load rebound was K103N (28). It would appear that maintaining trough plasma levels of efavirenz may delay the emergence of highly resistant viral variants (29).

The potential for the development of resistance to efavirenz *in vivo* has also been evaluated in patients enrolled in clinical trials of efavirenz in combination with the HIV protease inhibitor indinavir or the nucleoside reverse transcriptase inhibitors zidovudine/lamivudine (ZDV/3TC). Overall, the results suggest that treatment with efavirenz is not associated with novel reverse transcriptase gene mutations, even in patients showing viral load rebounds on efavirenz-containing regimens (30).

DuPont Merck is currently conducting wide-ranging clinical trials of efavirenz (Sustiva™) in HIV/AIDS patients. The company has broadened its Expanded Access Program to include patients who have or had at any time CD4 counts of less than 400 cells/mm^3. The drug is being administered in combination with at least one other marketed or investigational antiretroviral agent, with both drugs initiated at the same time. DuPont Merck plans to file an NDA for efavirenz during the second quarter of 1998 (31).

Manufacturer

DuPont Merck Pharmaceutical Co. (US).

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