Drugs 1998 Dec; 56 (6): 1055-1064
0012-6667/98/0012-1055/$10.00/0

Efavirenz

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Contents

Abstract

▲ Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI) which shows good inhibitory activity against HIV-1.

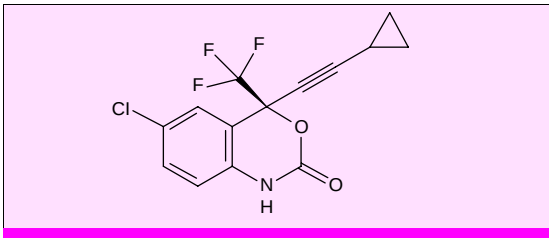
▲ Reduced susceptibility to efavirenz has been reported with HIV-1 variants containing single and multiple mutations to the reverse transcriptase enzyme. *In vitro* and *in vivo* data suggest that the resistance profile of efavirenz overlaps with that of the NNRTIs nevirapine and delavirdine.

▲ Clinically significant drug interactions have been reported with efavirenz and indinavir and saquinavir. An increase in dosage of indinavir from 800 to 1000mg 3 times daily is recommended during coadministration with efavirenz. Use of efavirenz in combination with saquinavir as the sole protease inhibitor is not recommended.

▲ Once-daily efavirenz in combination with zidovudine plus lamivudine or indinavir or nelfinavir increased CD4+ cell counts and reduced HIV RNA plasma levels to below quantifiable levels (<400 copies/ml) in HIV-infected patients. A sustained reduction in viral load was maintained for at least 72 weeks in 1 study.

▲ Nervous system symptoms (including headache, dizziness, insomnia and fatigue) and dermatological effects (including maculopapular rash) appear to be the most common adverse events reported with efavirenz-containing antiretroviral regimens.

Features and properties of efavirenz (DMP 266)	
Indication	
HIV infection	Approved
Mechanism of action	
Antiviral	Non-nucleoside HIV-1 reverse transcriptase inhibitor
Dosage and administration	
Usual dosage in clinical trials	200 to 600 mg/day as part of combination therapy
Route of administration	Oral
Frequency of administration	Once daily
Pharmacokinetic profile	
Maximum plasma concentration at steady state after administration of efavirenz 600mg once daily	4.1 mg/L
Area under the plasma concentration-time curve at steady state after administration of efavirenz 600mg once daily	58.1 mg/L • h
Elimination half-life	40 to 76h
Adverse events	
Most frequent	Nervous system symptoms (headache, dizziness, insomnia and fatigue), maculopapular rash



Efavirenz (DMP 266)

In the absence of a cure for HIV infection, the current aim of antiretroviral therapy is to produce maximal suppression of HIV replication for as long as possible. To achieve this goal and to minimise the development of drug resistance, current treatment guidelines recommend the use of combination therapy comprising for example 2 nucleoside reverse transcriptase inhibitors (NRTIs) with either a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor (NNRTI).[1,2]

Efavirenz (formerly DMP 266) is a benzoxazinone and an orally active NNRTI. It is currently under investigation as a component of combination antiretroviral therapy for HIV infection.

1. Pharmacodynamic Profile

In Vitro Anti-HIV Activity

- The inhibition constant (K_i) of efavirenz against wild type HIV-1 reverse transcriptase was 2.93 nmol/L.[3]

- Efavirenz demonstrated good inhibitory activity against wild-type HIV-1 replicative spread in primary lymphoid and monocytoid cell cultures [concentration producing 95% inhibition (IC_{95}) = 1.5 to 3.0 nmol/L].[3]

- Efavirenz has demonstrated synergistic inhibition of HIV-1 in cell culture when combined with zidovudine, didanosine or indinavir.[4]

- Efavirenz was cytotoxic in HIV-infected primary cells and in a T cell line at a concentration of 80 μmol/L.[3]

Viral Resistance

- Efavirenz K_i values against a panel of single-mutation reverse transcriptase enzymes with reduced susceptibility to other NNRTIs ranged from 2.97 to 17.60 nmol/L.[3] Against a pair of double-mutation reverse transcriptase enzymes with reduced susceptibility to other NNRTIs, efavirenz K_i values were 26.05 and 56.50 nmol/L.[3]

- In a study using 2 cell types (MT-2 T cells and peripheral blood mononuclear cells), 2 different multiple substitutions of the reverse transcriptase gene produced 2 highly efavirenz-resistant HIV-1 variants (V179D/L100I/Y181C and L100I/V108I). In MT-2 cells, 12, 15 and 24 serial passages of efavirenz resulted in 7-, 11- and 1000-fold increases in resistance to efavirenz (based on IC_{90} values with IC_{90} for wild-type HIV-1 used as a reference). One amino acid substitution (V179D) was identified by passage 15 and an additional 2 amino acid substitutions (L100I and Y181C) were identified by passage 24.[5]

- The IC_{50} for efavirenz against HIV-1 isolates from patients who had failed to respond to efavirenz-containing combination therapy was ≥20-fold that against pre-therapy viral isolates.[6] The mutations K103N and V108I and/or Y188L were present in the resistant isolate. The pattern of HIV-1 mutations was not influenced by the concomitant antiretroviral therapy taken by the patients.

- Data from *in vitro* and *in vivo* studies suggest that the resistance profile of efavirenz overlaps with that of other NNRTIs including nevirapine and delavirdine.[6,7]

- The potency of efavirenz against HIV-1 variants expressing single reverse transcriptase substitutions at codons 48, 108, 179, 181 and 236 was similar to that seen against wild type virus (assayed in MT-4 T cells).[3,7] Modest resistance (<10-fold) was observed against variants containing the mutations A98G, K101E, V106A, Y188C and G190A and this increased to 20- to 70-fold with the point mutations L100I and K103N.[3,7] Against HIV variants with the single amino acid change Y188L or the double amino acid substitutions S48T + G190S,

K101E + K103N, K101E + L100I and K103N + Y181C, a greater reduction in susceptibility to efavirenz was detected (>80- to 1000-fold).[3,7]

- In MT-4 T lymphoid cell cultures, 10 serial passages of HIV-1 IIIb under increasing selective pressure of efavirenz yielded a variant with ≈17 000-fold reduced susceptibility to the drug (IC_{95} 25 μmol/L *vs* IC_{95} 1.5 nmol/L for wild type HIV-1 IIIb).[3] Resistance to efavirenz in this variant was mediated via mutations at amino acids 100 (Leu→Ile) and 103 (Lys→Asn) of the reverse transcriptase enzyme.

2. Pharmacokinetic Profile

- Peak efavirenz plasma concentrations (C_{max}) of 0.51 to 2.9 mg/L were achieved 5 hours after single-dose oral administration of efavirenz 100 to 1600mg to healthy volunteers.[4] Although dose-related increases in C_{max} were reported, they were less than proportional, suggesting reduced absorption at higher doses.

- Efavirenz plasma concentrations reached steady-state levels within 6 to 10 days during administration of efavirenz 200, 400 or 600 mg/day to HIV-1-infected patients.[4] After administration of efavirenz 600mg once daily to HIV-infected individuals, efavirenz trough plasma concentrations, C_{max} and area under the efavirenz plasma concentration-time curve (AUC) at steady state were 1.8 mg/L, 4.1 mg/L and 58.1 mg/L · h, respectively.[4]

- Efavirenz crosses the blood-brain barrier. Efavirenz CSF concentrations were 0.26 to 1.19% of the corresponding plasma concentrations in 9 patients treated with efavirenz 200 to 600mg once daily for at least 1 month.[4]

- Efavirenz is highly bound to human plasma proteins (99.5 to 99.75%), mainly to albumin.[4]

- Efavirenz is metabolised in the liver, predominantly by the cytochrome P450 (CYP) 3A4 and 2B6 isoenzymes.[4] Hydroxylated metabolites are produced which have negligible antiviral activity.

- Approximately 14 to 34% of a radiolabelled dose of efavirenz 400mg was excreted in the urine in the form of metabolites and 16 to 61% was excreted in the faeces as unchanged drug.[4] Less than 1% of an administered dose of efavirenz is excreted unchanged in the urine.

- The terminal plasma elimination half-life of efavirenz was 52 to 76 and 40 to 55 hours, respectively, after single- and multiple-dose oral administration (dose not specified).[4]

Drug Interactions

- Efavirenz has been reported to induce CYP3A4 *in vivo*. In *in vitro* studies efavirenz inhibited the isoenzymes CYP2C9, 2C19 and 3A4. Thus, efavirenz may alter the metabolism of drugs by these enzymes. Similarly, the metabolism of efavirenz may be increased by drugs which induce CYP3A4, and efavirenz may also induce its own metabolism.[4]

- Coadministration of efavirenz 200mg once daily and indinavir 800mg 3 times daily for 14 days decreased the C_{max} and AUC of indinavir by 16 and 31%, respectively.[4] An increase in the dosage of indinavir from 800 to 1000mg 3 times daily is recommended in patients receiving concomitant efavirenz therapy.[4]

- Efavirenz 600mg once daily for 10 days greatly decreased the C_{max} (50%) and AUC (62%) of coadministered saquinavir (1200mg 3 times daily as soft gelatin capsules) in healthy volunteers.[4] Use of efavirenz in combination with saquinavir as the sole protease inhibitor is not recommended.

- In healthy volunteers given efavirenz 400mg once daily and clarithromycin 500mg twice daily for 7 days, the AUC of clarithromycin was decreased by 39% and the AUC of its hydroxy-metabolite was increased by 34%.[8]

- Significant mean decreases in the C_{max} (from 4.8 to 3.7 mg/L) and AUC of efavirenz (from 70.7 to 47.7 mg/L · h) were reported compared with monotherapy values in 10 of 12 healthy volunteers who received efavirenz 600mg and rifampicin 600mg both administered once daily for 7 days.[9] These decreases were attributable to induction of the metabolism of efavirenz by rifampicin. Conversely, the

pharmacokinetic profile of rifampicin did not appear to be appreciably affected by the coadministration of efavirenz.

- The AUC of a single 50μg dose of ethinyl estradiol was significantly increased by 37% in healthy female volunteers who received concomitant efavirenz 400mg once daily for 10 days.[4,10]

- Efavirenz did not show clinically significant pharmacokinetic interactions with fluconazole,[11] nelfinavir,[12,13] azithromycin,[8] the combination of zidovudine and lamivudine[4] or single doses of aluminium/magnesium hydroxide antacid or famotidine[14] in healthy volunteers or HIV-infected patients.

- Monitoring of liver enzymes is recommended in patients receiving concomitant efavirenz and ritonavir.[4,15]

3. Therapeutic Trials

Clinical trials with once-daily efavirenz have included both antiretroviral therapy-naive and experienced patients. The available data from these trials are based on surrogate marker end-points.

Efavirenz plus Lamivudine and Zidovudine

- In a double-blind study (protocol DMP 266-004), 63 patients (HIV RNA ≥2500 copies/ml) received efavirenz 400 or 600mg once daily or placebo in addition to their existing combination therapy comprising zidovudine plus lamivudine. At 16 weeks, the percentage of patients with HIV RNA plasma levels <400 copies/ml was relatively low, 23, 33 and 4%, respectively (fig. 1).[16,17] Duration of response was short but significantly longer in the efavirenz 600 mg/day group (median time to treatment failure 10 weeks) than in the efavirenz 400 mg/day group.[16,17]

- In a randomised, double-blind study (protocol DMP 266-005) in antiretroviral therapy-naive patients, a significantly greater percentage of patients treated with efavirenz (200, 400 or 600 mg/day) plus zidovudine and lamivudine for 16 weeks achieved HIV RNA plasma levels <400 copies/ml than patients treated with placebo plus zidovudine and lamivudine (fig. 1).[18,19] A corresponding significant increase in mean CD4+ cell count from baseline was reported in all 4 treatment groups.

- A significantly greater percentage of patients treated with efavirenz plus zidovudine and lamivudine achieved HIV RNA plasma levels <400 copies/ml than patients treated with indinavir in combination with zidovudine and lamivudine for 24 weeks in a nonblind randomised study (protocol DMP 266-006) [fig. 1].[20,21] Viral suppression was also greater with efavirenz plus indinavir therapy than with indinavir plus zidovudine and lamivudine in this study (fig. 1); however, a statistically significant difference was not reported. Increases in CD4+ cell counts were similar in the 3 treatment groups. At 36 weeks, the percentage of patients achieving HIV RNA plasma levels <50 copies/ml was significantly in favour of efavirenz plus zidovudine and lamivudine compared with the indinavir plus zidovudine and lamivudine treatment regimen (66 *vs* 50%; $p \leq 0.05$).[21]

- In the above study, CSF HIV RNA levels were reduced to <400 copies/ml in 8 of 8 patients after 16 weeks' treatment with efavirenz in combination with indinavir or with zidovudine plus lamivudine.[22]

Efavirenz plus Indinavir

- After 72 weeks' therapy, a significantly greater percentage of asymptomatic or mildly symptomatic patients treated with efavirenz plus indinavir had HIV RNA plasma levels <400 copies/ml than individuals receiving indinavir initially as monotherapy and then in combination with efavirenz and stavudine (study DMP 266-003, cohort IV) [fig. 2].[23,24] Mean reductions in HIV RNA plasma levels were 2.3 and 1.8 $\log_{10}$ copies/ml, respectively ($p \leq 0.01$). Although patients randomised to the latter treatment group initially received indinavir monotherapy, efavirenz and stavudine were subsequently added to therapy at 12 weeks because of concerns regarding the appropriateness of antiretroviral monotherapy.[23,24]

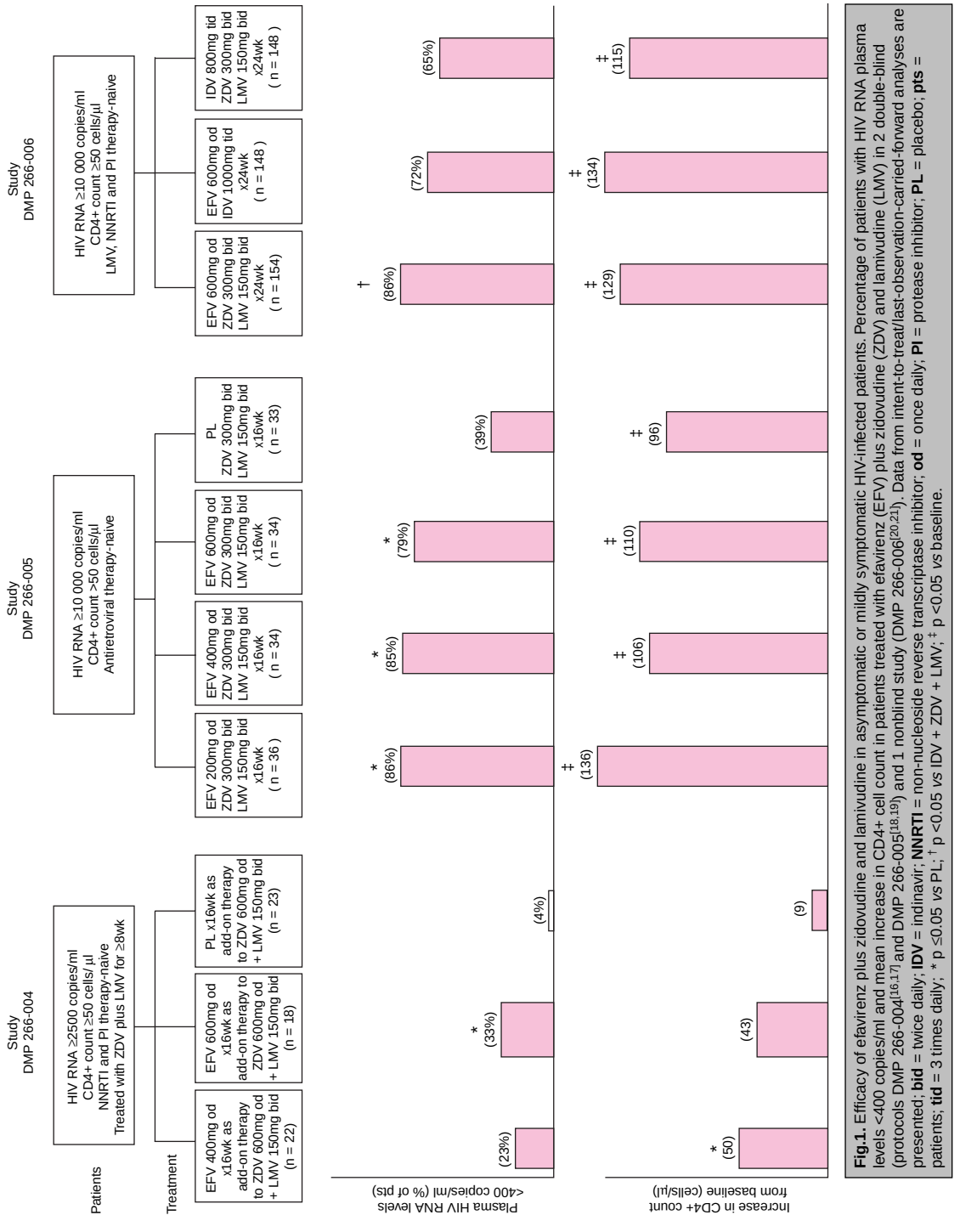


Fig.1. Efficacy of efavirenz plus zidovudine and lamivudine in asymptomatic or mildly symptomatic HIV-infected patients. Percentage of patients with HIV RNA plasma levels <400 copies/ml and mean increase in CD4+ cell count in patients treated with efavirenz (EFV) plus zidovudine (ZDV) and lamivudine (LMV) in 2 double-blind (protocols DMP 266-004[16,17] and DMP 266-005[18,19]) and 1 nonblind study (DMP 266-006[20,21]). Data from intent-to-treat/last-observation-carried-forward analyses are presented; **bid** = twice daily; **IDV** = indinavir; **NNRTI** = non-nucleoside reverse transcriptase inhibitor; **od** = once daily; **PI** = protease inhibitor; **PL** = placebo; **pts** = patients; **tid** = 3 times daily; * $p \leq 0.05$ *vs* PL; † $p < 0.05$ *vs* IDV + ZDV + LMV; ‡ $p < 0.05$ *vs* baseline.

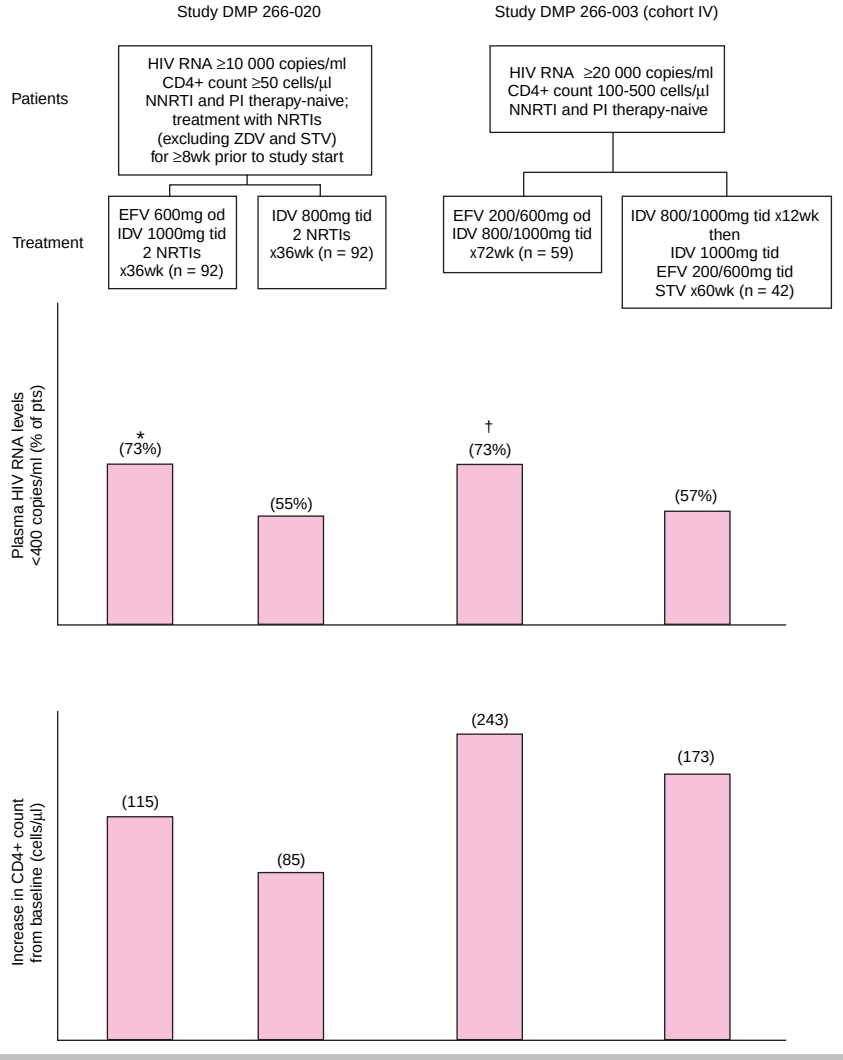


Fig. 2. Efficacy of efavirenz plus indinavir. Percentage of patients with HIV RNA plasma levels <400 copies/ml and mean increase in CD4+ cell count in patients treated with efavirenz (EFV) plus indinavir (IDV) in 2 randomised double-blind studies (protocol DMP 266-020[25,26] and DMP 266-003[23,24]). Data from intent-to-treat/last-observation-carried-forward analyses are presented. In study DMP 266-020 patients were permitted to switch NRTIs if they met protocol-specific treatment failure criteria. In study DMP 266-003 the dose of EFV was increased to 600 mg/day after 36 weeks and the dose of IDV was increased to 1000mg 3 times daily (tid) before 12 weeks in all patients. **NNRTI** = non-nucleoside reverse transcriptase inhibitor; **NRTI** = nucleoside reverse transcriptase inhibitor; **od** = once daily; **PI** = protease inhibitor; **pts** = patients; **STV** = stavudine; **ZDV** = zidovudine; * $p < 0.05$ *vs* IDV + 2 NRTIs; † $p = 0.038$ *vs* IDV + EFV + STV.

• In a double-blind study (protocol DMP 266-020), a significantly greater proportion of patients treated with efavirenz plus indinavir and 2 NRTIs had HIV RNA plasma levels <400 copies/ml than patients treated with indinavir plus 2 NRTIs for 36 weeks (fig. 2).[25,26] Furthermore, the 4-drug combination (containing efavirenz) reduced plasma HIV RNA levels to <50 copies/ml in a significantly greater percentage of patients than the 3-drug combination (including indinavir) [54 *vs* 37%; $p < 0.05$]. Mean

reductions in HIV RNA plasma levels from baseline were 2.3 and 1.6 log_{10} copies/ml, respectively ($p < 0.05$). There was also a trend towards a greater increase in CD4+ cell count with the 4-drug regimen (fig. 2).

Efavirenz plus Nelfinavir

- Treatment with efavirenz 600mg once daily plus nelfinavir 750mg 3 times daily for 16 weeks produced a significant reduction in plasma HIV RNA levels from baseline (≈1.6 log_{10} copies/ml) in both antiretroviral therapy-naive and NRTI-experienced patients (study DMP 266-024) [fig. 3].[27,28] 81 and 63% of patients, respectively, achieved HIV RNA plasma levels <400 copies/ml and a corresponding increase in CD4+ cell count was also reported in both patient groups (fig. 3). At 24 weeks, 71 and 46% of NRTI-naive and -experienced patients, respectively, had HIV RNA plasma levels <50 copies/ml.[28]

- After 16 weeks' treatment, virological suppression was significantly superior with efavirenz plus nelfinavir plus 2 NRTIs to that with a 3-drug combination comprising efavirenz or nelfinavir plus 2 NRTIs in NRTI therapy-experienced patients (protocol ACTG 364) [fig. 3].[29,30] Significant increases in CD4+ cell counts from baseline were reported in all 3 treatment groups.

- HIV RNA plasma levels were <400 copies/ml in 63% of children after 20 weeks' treatment with efavirenz 600 mg/m^2 once daily plus nelfinavir 20 to 30 mg/kg 3 times daily and NRTIs (dosages not

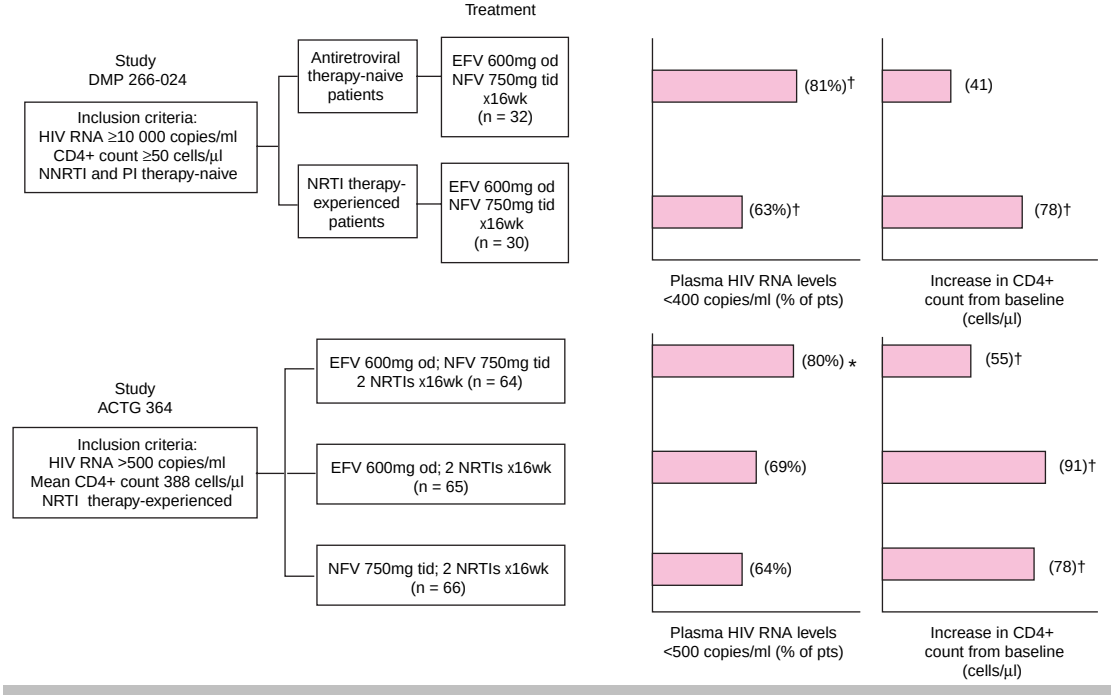


Fig. 3. Efficacy of efavirenz plus nelfinavir. Percentage of patients with HIV RNA plasma levels <400 copies/ml and mean increase in CD4+ cell count in HIV-infected patients treated with efavirenz (EFV) plus nelfinavir (NFV) with or without nucleoside reverse transcriptase inhibitors (NRTIs) in a nonblind (protocol DMP 266-024[27,28]) and a randomised double-blind study (ACTG 364[29,30]). Data for HIV RNA levels (DMP 266-024 and ACTG 364) and CD4+ cell count (DMP 266-024) are from intent-to-treat/last-observation-carried-forward analyses. **NNRTI** = non-nucleoside reverse transcriptase inhibitor; **od** = once daily; **PI** = protease inhibitor; **pts** = patients; **tid** = 3 times daily; * $p < 0.05$ *vs* EFV or NFV plus 2 NRTIs; † $p < 0.05$ *vs* baseline.

specified).[31,32] All children enrolled in this multicentre study (protocol ACTG 382; n = 57) were aged <16 years, protease inhibitor and NNRTI therapy-naive and had a median HIV RNA plasma level of 10 000 copies/ml and a median CD4+ cell count of 699 cells/μl.

Efavirenz Monotherapy

- HIV RNA plasma levels were decreased from baseline by a mean of 1.68 $\log_{10}$ copies/ml (98% viral suppression) and CD4+ cell count was increased by 96 cells/μl in HIV-1 infected patients (n = 11; CD4+ cell count 200 to 500 cells/μl and HIV RNA plasma levels >20 000 copies/ml) treated with efavirenz 200mg once daily for 2 weeks (study DMP 266-003 cohort I to III).[33] These parameters did not change significantly from baseline among patients randomised to the placebo treatment group (n = 5).

4. Tolerability

- In a large randomised study (n = 450), nervous system symptoms (including headache, dizziness, insomnia and fatigue) and dermatological effects (including maculopapular rash) were the most frequent adverse events associated with combination regimens including efavirenz.[20,34] Other commonly reported adverse effects included nausea and vomiting, dyspepsia and diarrhoea (fig. 4).

- In the above study, efavirenz-containing regimens (efavirenz plus indinavir or efavirenz plus zidovudine and lamivudine) were associated with a significantly higher incidence of nervous system symptoms (48 and 54% *vs* 21%; $p < 0.05$) and rash (33 and 29% *vs* 14%; $p < 0.05$) compared with treatment comprising indinavir plus zidovudine and lamivudine.[34] In contrast, the incidence of nausea and vomiting (3 to 10 *vs* 13 and 22%) and pain (0 and 1% *vs* 10%) was significantly lower with both efavirenz-containing regimens ($p \leq 0.05$). Discontinuation rates due to nervous system or dermatological adverse effects in the efavirenz treatment groups were 1 to 2%.

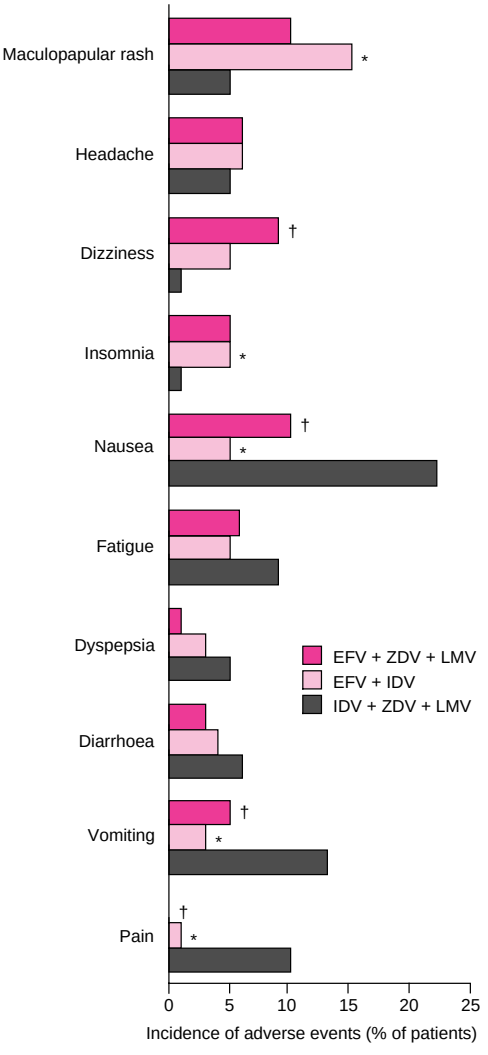


Fig. 4. Tolerability of efavirenz (EFV)-containing combination regimens.[20,21] 450 patients received 1 of 3 treatment regimens for 24 weeks: EFV 600mg once daily plus indinavir (IDV) 1000mg 3 times daily; EFV 600mg once daily plus zidovudine (ZDV) 300mg twice daily and lamivudine (LMV) 150mg twice daily; IDV 800mg 3 times daily plus ZDV 300mg twice daily and LMV 150mg twice daily. Adverse events possibly or probably treatment related and occurring in ≥5% of patients are shown. *$p \leq 0.05$ EFV + IDV *vs* IDV + ZDV + LMV; †$p \leq 0.05$ EFV + ZDV + LMV *vs* IDV + ZDV + LMV.

• Nervous system symptoms and dermatological adverse effects associated with efavirenz therapy appear to be generally mild to moderate in severity, with a median duration of 12 to 21 days.[34] Administration of efavirenz at bedtime appeared to reduce the severity and duration of nervous system symptoms, and rashes were effectively managed using antihistamines and topical corticosteroids.[20]

5. Efavirenz: Current Status

Efavirenz is a once-daily NNRTI which has recently been approved in the US for use in combination with other antiretrovirals for the treatment of HIV infection. In combination with other antiretroviral agents including NRTIs and/or protease inhibitors, efavirenz reduced plasma HIV RNA titres to below quantifiable levels in many patients. Furthermore, a sustained reduction in viral load (up to 72 weeks) has been reported with a combination regimen comprising efavirenz plus indinavir.

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