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Efavirenz – Still First Line King?

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Abstract

Background—Efavirenz is a potent, safe and tolerable non-nucleoside reverse transcriptase inhibitor (NNRTI) recommended as initial therapy. Recently, several new antiretroviral drugs, including second generation NNRTIs, protease-inhibitors, an integrase-inhibitor and a CCR5 inhibitor, have become or will be shortly available.

Objective—This article will review relevant efficacy and safety data of efavirenz compared to these novel agents or certain common alternate drugs currently used as initial therapy in treatment-naïve patients.

Methods—Published articles and conference presentations pertaining to efavirenz and/or the newer antiretroviral agents were evaluated.

Results/Conclusions—Efavirenz will continue to be preferred initial therapy for now. If longer-term studies of integrase inhibitors and second-generation NNRTIs confirm initial findings, they will eventually supplant efavirenz as preferred first-line agents.

Keywords

efavirenz; treatment naïve; novel antiretroviral agents

1. Introduction

Highly-active combination antiretroviral therapy has dramatically reduced HIV-related morbidity and mortality. Nevertheless, current treatment regimens are limited by intolerance, short- and long-term toxicities and emergence of drug resistance. Typical regimens include two nucleoside reverse transcriptase inhibitors (NRTIs) and either a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI). Efavirenz, an NNRTI FDA-approved in 1998, quickly became widely-used in developed countries. Current guidelines recommend efavirenz with two NRTIs, either abacavir/lamivudine or emtricitabine/tenofovir, as preferred first-line regimens for treatment-naïve patients[1].

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Efavirenz has a low pill burden, once daily dosing, absence of some adverse effects associated with PIs, and a long half-life allowing for relatively stable plasma concentrations and some forgiveness for doses not taken exactly on schedule. It is available in combination with emtricitabine and tenofovir as a single tablet, which is an ideal regimen for treatment-naïve patients. Drawbacks of efavirenz include neuropsychiatric adverse effects, teratogenicity, many clinically significant drug interactions, and a low genetic barrier to the development of drug-resistant viral mutants.

2. Efavirenz

2.1 Chemistry

Efavirenz is available in the U.S. alone (Sustiva®) or co-formulated with emtricitabine and tenofovir (Atripla™). Sustiva® is marketed in the U.S. as 50 mg and 200 mg capsules as well as 600 mg film-coated tablets, all for oral administration. Atripla™ is manufactured in the U.S. as film-coated tablets containing 600 mg efavirenz, 200 mg emtricitabine, and 300 mg tenofovir disoproxil fumarate.

Efavirenz is an HIV-1 specific, non-nucleoside reverse transcriptase inhibitor. The chemical name is (S)-6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2H-3,1-benzoxazin-2-one, with a molecular formula of $C_{14}H_9ClF_3NO_2$ and a molecular mass of 315.68 (Figure 1)[2].

Efavirenz non-competitively inhibits wild-type HIV-1 reverse transcriptase. However, it does not inhibit human cellular DNA polymerases α, β, γ and δ[3]. *In vitro* activity of efavirenz against laboratory adapted and clinical isolates of HIV-1 demonstrate 90 – 95% inhibitory concentrations of 0.5 – 8 ng/mL. Efavirenz displayed additive antiviral activity when combined with other NRTIs, NNRTIs and PIs, except for atazanavir, where it showed additive to antagonistic activity[2]. Efavirenz is active against HIV-1 subtypes A, AE, AG, C, D, F, G, J, and N, but it is not active against HIV-2, simian immunodeficiency virus, and has reduced activity against group O viruses[4].

2.2 Pharmacokinetics, Metabolism and Interactions

Efavirenz bioavailability is 40 – 45 % without food, with maximum concentrations (C_{max}) reached within 2 – 5 hours. Food increases efavirenz AUC and C_{max} by 15 – 30% and 40 – 80%, respectively. Standard doses of 600 mg by mouth once daily reach steady-state in 1 – 2 weeks, with maximum and minimum concentrations of 3 – 4.3 mcg/mL and ~ 1.5 mcg/mL, respectively[5, 6]. Mean efavirenz AUC, oral clearance and apparent volume of distribution are 55 – 60 mcg•hr/mL, 10 – 12 L/hr, and 280 – 500 L, respectively[5–7]. Efavirenz is extensively protein-bound (>99%), primarily by albumin. It has a long terminal half-life, 35 – 50 hours. Because of this long half-life, efavirenz may persist at low concentrations for several days to weeks after stopping treatment potentially allowing viral resistance to develop. Some experts recommend stopping efavirenz 1 – 2 weeks prior to stopping the rest of the antiretrovirals; however, the optimal time sequence for stopping each component of antiretroviral therapy is unknown.

Efavirenz is rapidly hydroxylated by cytochrome P450 (CYP) 2B6, and more slowly by CYP 3A4, to metabolites that are glucuronidated and eliminated. Patients with hepatic impairment or hepatitis B or C infection should be monitored carefully when starting efavirenz. Since < 1% of efavirenz is eliminated in the urine, no dose adjustment is necessary in renal impairment. Efavirenz induces CYP 3A4 metabolic activity *in vivo*, causing decreased exposure to drugs metabolized by this enzyme. Efavirenz exposure may also be affected by medications which greatly alter CYP 3A4 activity, since this is a secondary pathway of efavirenz metabolism[2]. Some efavirenz drug interactions may be overcome by altering doses of the affected drugs. Also, efavirenz has fewer significant drug interactions than a ritonavir-boosted regimen, as ritonavir induces and inhibits to a larger extent a wider variety of CYP enzymes. An allelic variant of CYP 2B6 (T/T genotype at position 516) is associated with higher efavirenz concentrations and increased frequency of central nervous system toxicities[8]. Therapeutic drug monitoring of efavirenz may be warranted, and the suggested mid-dosing interval plasma concentrations should fall within 1 – 4 mcg/mL[9–12]. Dose reductions in patients with high efavirenz concentrations may attenuate exposure-related adverse effects. One difficulty of individualizing an efavirenz dose is that the pill burden may increase if the patient needs to switch to a dose other than 600 mg daily.

2.3 Resistance

High level resistance to efavirenz can develop with a single mutation[3]. The K103N mutation is frequently the first resistance mutation selected during treatment with efavirenz, and confers up to 100 fold loss of potency. With continued treatment, most patients develop additional viral mutations such as L100I, V106M, V108I, Y181C/I, Y188L, G190A/S, and P225H[13, 14]. Because of polymorphisms in the viral reverse transcriptase gene between HIV subtypes, patients with clade C virus may develop different resistance mutations (K103E, V179D, and Y188C/H, for example); these also confer high-level resistance[15–17]. Cross-resistance occurs between nevirapine, efavirenz and delavirdine, but does not occur with NRTIs or second generation NNRTIs. In fact, some NRTI mutations confer hypersusceptibility to NNRTI (118I, 208Y, 215Y)[18–20], though the clinical relevance has not been fully elucidated. Resistance mutations to NNRTI are genotypically detectible in most patients more than a year after stopping the drug. Mutations likely persist indefinitely in archived quasispecies even when they below the genotype level of detection. Furthermore, patients failing an initial NNRTI-based regimen consistently have a greater number viral resistance mutations than patients failing an initial PI-based therapy[21]. Hence, patients who fail an NNRTI-based regimen will have fewer treatment options for future regimens.

Transmission of resistant virus is of growing concern. The percentage of treatment-naïve subjects already harboring NNRTI-resistant virus varies among different geographic regions, but has been generally increasing to the current rates of 10 – 15 % in Europe and the United States[22, 23]. Rates of primary resistance as high as 20% have been noted in the United Kingdom[23]. With continued widespread use of efavirenz as first-line therapy, these rates are expected to continue to increase, and the first-generation NNRTIs will be effective in a much smaller subset of treatment-naïve patients.

3. Safety and Tolerability

The adverse effect profile of efavirenz is well-characterized, including dermatologic, gastrointestinal, hepatic, lipidemic, and central nervous system manifestations (Table 1)[24–26]. A mild-to-moderate maculopapular rash occurs in 2 – 10% of patients, usually within the first few weeks and resolving within a month without discontinuing therapy. Severe skin rash is rare, and efavirenz should be discontinued if it occurs. Nausea, diarrhea and vomiting occur in up to 13% of patients, and liver enzyme increases are seen in 2 – 7%. Efavirenz can increase HDL-cholesterol, total cholesterol and triglycerides, although to a lesser extent than PIs.

Neuropsychiatric adverse events occur in up to half of patients within the first few days to weeks of efavirenz therapy[8, 27–29]. Symptoms include abnormal dreams, insomnia, somnolence, hallucinations, dizziness and impaired concentration. These resolve spontaneously in most patients, with < 5% requiring discontinuation due to severe adverse effects (aggressive behavior, severe depression, suicidal thoughts, and paranoia). These self-limited neuropsychiatric side effects are the main reason that efavirenz is typically dosed at bedtime instead of in the morning. Mild-to-moderate neuropsychiatric symptoms do persist in some patients for months or even years after starting efavirenz[28, 29].

Efavirenz is teratogenic to laboratory animals, with severe neural tube defects in primates receiving efavirenz early in pregnancy[2]. A case report documented that an infant exposed to efavirenz *in utero* had a neural tube defect[30]. The Antiretroviral Pregnancy Registry has prospectively documented 8 birth defects (not neural tube defects) in 321 live births, and retrospectively reported 5 cases of neural tube defects[2]. Efavirenz is pregnancy category D, and should not be used in early pregnancy[31].

4. Clinical Efficacy

Historically, efavirenz-based regimens have proven superior to triple NRTI therapy[32], and equivalent or modestly superior to nevirapine[26]. Several recent reviews provide a detailed description of these findings[33–35]. In recent comparative trials of new antiretroviral agents from multiple drug classes efavirenz continues to demonstrate excellent efficacy (Table 2). However, several drawbacks to efavirenz include a low genetic barrier to resistance, adverse neuropsychiatric effects and increased effects on total cholesterol and triglycerides compared to these newer agents (Table 1). Additionally, efavirenz is teratogenic and may not be an appropriate first-line agent for women of child-bearing age, especially considering that half of all pregnancies in the U.S. are unintended (unplanned), and women in resource-poor settings often do not have access or rights to effective contraception.

4.1 Efavirenz vs. Protease-Inhibitors in Treatment-Naïve Patients

Viral load reduction in treatment-naïve patients taking efavirenz is superior to that seen with unboosted indinavir and nelfinavir[36, 37]. However, similar rates of viral suppression were observed between efavirenz and the newer unboosted PI, atazanavir[25]. After 48 weeks, the proportion of subjects achieving viral suppression was similar for those receiving atazanavir 400 mg once-daily or efavirenz (below 400 copies/mL: 70% vs. 64%; below 50 copies/mL:

32% vs. 37%%). While rates of treatment discontinuation due to intolerance were similar between efavirenz and atazanavir (20% vs. 16%, respectively), subjects taking efavirenz had a higher incidence of rash and dizziness while atazanavir was associated with increased jaundice. Further, efavirenz-treated subjects had significantly greater increases from baseline for total cholesterol (mean change: +21% vs. +2.0%; P<0.001) and triglycerides (+23% vs. −9.0%; P<0.001).

Comparisons between efavirenz- and lopinavir/ritonavir-based regimens have been less clear-cut. In one study, virologic response was similar between efavirenz and lopinavir/ritonavir. Interestingly, CD4+ cell count recovery was greater in the lopinavir/ritonavir group[38], which is consistent with other reports of improved immune recovery with PI- versus efavirenz-based regimens[39]. The most definitive study to date comparing efavirenz to lopinavir/ritonavir is A5142[40]. This prospective study randomized 753 treatment-naïve patients to either lopinavir/ritonavir (400/100 mg twice- daily) or efavirenz (600 mg once-daily) combined with lamivudine and a second NRTI, or a NRTI-sparing regimen of lopinavir/ritonavir (533/133 mg twice-daily) and efavirenz (600 mg once-daily) for 96 weeks. The co-primary endpoints of the study were to compare, pairwise between the three treatment arms, the time to virologic failure (lack of suppression of plasma HIV-1 RNA by 1 $\log_{10}$ or rebound before Week 32, or failure to suppress to < 200 copies/mL or rebound after Week 32) and the time to regimen completion (either virologic failure or toxicity-related discontinuation). The adjusted significance level for multiple comparisons between arms and an interim analysis was α=0.016. At Week 96, the treatment failure rate for efavirenz was significantly lower than for lopinavir (24% vs. 33%; P=0.006). Further, a greater proportion of patients in the efavirenz arm had HIV RNA levels < 50 copies/mL at Week 96 than the lopinavir group (89% vs. 77%; P=0.003, respectively). However, increases in CD4+ cell count were greater for the lopinavir/ritonavir group (+268 vs. +241 at 96 weeks, p=0.01). Also, the efavirenz-treated subjects who failed therapy had a greater number of resistance mutations than lopinavir/ritonavir-treated subjects who experienced virologic failure. Lopinavir/ritonavir-treated subjects had greater increases in total cholesterol than efavirenz-treated subjects (47 mg/dL vs. 14 mg/dL, P<0.01). In contrast, efavirenz-treated subjects had a higher proportion of protocol-defined lipoatrophy than the lopinavir/ritonavir group (32% vs. 18%, P<0.01)[41].

Darunavir is a PI, recently approved for treatment-experienced patients with extensive HIV drug resistance[42]. Although no comparative trials with efavirenz have been conducted, darunavir holds strong potential as a new therapeutic option for treatment- naïve patients. The ARTEMIS trial randomized 689 treatment-naïve subjects to darunavir/ritonavir (800/100mg once-daily) or lopinavir/ritonavir (400/100 mg twice-daily or 800/200 mg once-daily) plus tenofovir/emtricitabine for 48 weeks. Darunavir-treated patients (N=343) had a similar proportion with viral suppression to the twice-daily lopinavir/ritonavir (N=267) arm (HIV RNA below 50 copies/mL: 84% vs. 81%, respectively), and a significantly greater response than once-daily lopinavir/ritonavir (N=52) treated subjects (HIV RNA below 50 copies/mL: 84% vs. 71%, respectively; P<0.05). Compared to the combined lopinavir/ritonavir arm, darunavir-treated subjects had significantly fewer grade 2 to 4 total cholesterol gains (23% vs. 13%) and fewer grade 2 to 4 triglyceride gains (11% vs. 3%). Comparative trials of darunavir with efavirenz in treatment-naïve patients are warranted.

4.2 Efavirenz versus Raltegravir in Treatment-Naïve Patients

Raltegravir is the first agent approved in the new drug target class of strand-transfer inhibitors of HIV-1 integrase (integrase inhibitors), and was evaluated in 160 treatment-naïve subjects at doses ranging from 100 mg to 600 mg twice daily in combination with tenofovir/lamivudine, and compared to 38 treatment-naïve subjects randomized to standard dose efavirenz plus tenofovir/lamivudine over 48 weeks[43]. The primary endpoint was the proportion of patients achieving plasma HIV-1 RNA < 400 copies/mL at week 24. Of note, this study was not powered to perform formal efficacy comparisons between raltegravir and efavirenz. No difference was seen between groups for the primary endpoint. Likewise, 85 – 95% of subjects achieved viral loads < 50 copies/mL in the raltegravir arms, and 92% met that goal in the efavirenz arm. These reductions in viral load persisted through 48 weeks of therapy for 83 – 98%, again with no difference between groups. Virologic failure occurred in 3% of subjects taking raltegravir and in 3% of efavirenz-arm subjects. Mean increases in CD4+ T-cell counts were similar across groups, at 144 – 221 cells/mm^3.

The notable differences between raltegravir and efavirenz were in the safety profiles and the rapidity of treatment response. Patients taking any dose of raltegravir achieved a viral load < 50 copies/mL earlier than patients taking efavirenz ($p < 0.05$). While the incidence of serious adverse events was similar with raltegravir arms (5% overall) and the efavirenz arm (5%), drug-related adverse events were less common in the raltegravir arms than in the efavirenz arm. Total cholesterol, low-density lipoprotein and triglyceride levels were unchanged over 48 weeks in the raltegravir groups. By contrast, all three of these increased in the efavirenz subjects. High-density lipoprotein increased in all subjects, with larger increases in those treated with efavirenz.

4.3 Efavirenz versus Maraviroc in Treatment-Naïve Patients

Maraviroc selectively and reversibly binds to the human chemokine receptor CCR5, preventing the interaction of HIV gp120 and the entry of CCR5-tropic HIV-1 into cells. The Merit study was a phase 3, prospective study of maraviroc in antiretroviral-naïve patients with R5 virus[44]. Subjects were randomized to either efavirenz (600mg once-daily or maraviroc (300mg twice-daily) in combination with zidovudine/lamivudine for 48 weeks. In the primary analysis, patients receiving efavirenz (n=361) had greater rates of viral suppression (HIV RNA <50 copies/mL) compared to patients treated with maraviroc (n=360; 69.3% versus 65.3%, respectively). Despite a greater percentage of virally-suppressed subjects in the efavirenz arm, those receiving maraviroc experienced significantly greater CD4 recovery at 48 weeks (mean CD4 gain: 169 vs. 142 cells/mm^3; difference of 27, 95% CI 7 – 46). In addition, the rate of discontinuation due to adverse events was less in the maraviroc (4.2%) than efavirenz-treated subjects (13.6%). Of note, a coreceptor tropism assay must be performed prior to starting a CCR5 antagonist such as maraviroc, which is an added expense compared to other antiretrovirals.

4.4 Second Generation Non-Nucleoside Reverse Transcriptase Inhibitors

Second-generation NNRTIs are active against virus resistant to first-generation NNRTIs. Additionally, they require multiple mutations before their activity is reduced. Etravirine (TMC125) is currently indicated only in treatment-experienced HIV-infected adults at a dose

of 200 mg twice daily. A clinical trial evaluating etravirine 400 mg once daily in treatment-naïve patients is ongoing. Etravirine is metabolized by cytochrome P450 enzymes (3A4, 2C9 and 2C19). It induces the activity of 3A4, and inhibits 2C9 and 2C19, and has the potential for significant drug interactions. Rash and nausea/vomiting are the most commonly-reported adverse effects in treatment-experienced patients taking etravirine[45, 46]. Other side effects occurred at rates similar to placebo, suggesting a lower propensity for central nervous system side effects and lipid alterations. Animal studies have not shown reproductive toxicity with etravirine, but no human data are available yet. No comparative studies with efavirenz are available.

Rilpivirine (TMC278) is an investigational second-generation NNRTI being studied in treatment-experienced and treatment-naïve subjects. Interim week 48 results of a 3-year comparative study of rilpivirine versus efavirenz in treatment-naïve subjects showed similar viral load reductions and CD4 cell count changes between the two groups[47]. Nausea rates were similar with the two agents, while central nervous system side effects and rash were significantly more common with efavirenz than with rilpivirine. Also, total and LDL cholesterol did not change in rilpivirine subjects while they increased in efavirenz-treated subjects. Unlike efavirenz, rilpivirine has not displayed teratogenic effects in studies conducted to date.

5. Conclusion

Efavirenz is an attractive first-line agent in treatment-naïve HIV-infected patients. It is dosed once daily, and comes in combination with NRTIs. The common adverse effects, rash and neuropsychiatric symptoms, are generally mild-to-moderate, and for many subjects, decrease over the first few weeks of continued therapy.

Extensive literature supports the virologic and immunologic efficacy of efavirenz regimens. Efavirenz is more potent than unboosted PIs, and has even shown superiority in some studies over lopinavir/ritonavir in viral load reduction. However, immunologic recovery in these studies was better in the lopinavir/ritonavir arms. The overall viral load reduction and CD4+ T-cell count recovery are similar, and efavirenz is considered to have similar efficacy to boosted PIs, with a better tolerability profile.

Toxicities of concern with long-term, widespread use of efavirenz include an adverse impact on total cholesterol, LDL and triglycerides. Another concern for use in women of child-bearing age is the documented teratogenicity in humans. This has limited efavirenz use worldwide in resource-poor settings. Even in developed countries, unintended pregnancies occur frequently, and efavirenz may not be an ideal choice in any woman of child-bearing age. Finally, efavirenz is a substrate of multiple cytochrome P450 enzymes, and a modulator of P450 enzyme activity; therefore, it is prone to many significant drug interactions.

A well-known characteristic of first-generation NNRTIs is the low genetic barrier to resistance development. A single mutation can drastically reduce the effectiveness of these agents. This can be an argument in favor of using these agents first-line. Once resistance develops, other PI-based regimens will still be active. Integrase inhibitors and second-line

NNRTIs can then also be used sequentially after a first-generation NNRTI-based regimen fails, which provides more options for treatment-experienced patients. However, patients who fail an NNRTI-based initial regimen often have a greater number of viral resistance mutations as compared to patients failing a PI-based initial regimen, leaving fewer future treatment options for those who started with an NNRTI. Additionally, with the widespread use of NNRTIs over the past several years, transmission of resistant virus has increased, limiting even the initial treatment options for some patients.

An alternative approach being studied is to use these newer agents instead of efavirenz as first-line therapy in treatment-naïve patients. For raltegravir, week 24 and 48 virologic and immunologic efficacy were similar to efavirenz in treatment-experienced patients, although raltegravir appears to suppress viral replication more quickly than efavirenz. Furthermore, the side effect profile of raltegravir seems to lack adverse lipid and neuropsychiatric effects. Results from on-going treatment-naïve studies are needed to confirm that raltegravir is as potent as efavirenz, but more tolerable.

Etravirine and rilpivirine are also being studied as first-line therapy in treatment-naïve patients. Efavirenz could remain the NNRTI of choice even after these study results are reported and the agents approved for use in treatment-naïve patients. The rationale would be to use efavirenz in first, and then still have the option of a salvage NNRTI regimen if the efavirenz regimen fails. However, using etravirine after an initial efavirenz or nevirapine-based regimen is not as effective as using a boosted PI in the second regimen[48], so the newer NNRTIs will likely only be used as a second regimen in NNRTI-experienced patients when PI regimens cannot be tolerated.

Initial results suggest second-generation NNRTIs have improved adverse effect profiles over efavirenz, again lacking the neuropsychiatric and lipid effects. Further, with the higher genetic barrier to resistance, etravirine and rilpivirine could be more durable in suppressing viral replication than first-generation NNRTIs. If longer-term studies indeed show similar efficacy to and improved tolerability over efavirenz, with or without improved durability of viral suppression, then these agents will likely supplant efavirenz as the NNRTI of choice of treatment-naïve patients. If these second-line agents also show no teratogenicity and no hepatic failure, their uptake worldwide to replace nevirapine, particularly for prevention of mother-to-child transmission of HIV, would be a natural consequence if their cost is not prohibitive.

6. Expert Opinion

Is efavirenz still the drug of choice for treatment-naïve patients? Yes. Efavirenz will remain the drug of choice in treatment-naïve patients in developed countries for the next several years. The vast amount of literature documenting efavirenz's safety and efficacy will be difficult for newer agents to rapidly overcome. The ease of adherence, with a low pill burden and once-daily dosing, are further advantages of efavirenz. However, if the initial study results of integrase inhibitors and second-generation NNRTIs continue to show similar efficacy to efavirenz and less toxicity in the longer-term studies, these agents will become very attractive first-line agents and will probably supplant efavirenz in developed countries.

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Abbreviations

AUC	area under the curve
CYP	cytochrome P450
FDA	Food & Drug Administration
HDL	high density lipoprotein
HIV	human immunodeficiency virus
NRTI	nucleoside reverse transcriptase inhibitor
NNRTI	non-nucleoside reverse transcriptase inhibitor
PI	protease inhibitor
U.S.	United States

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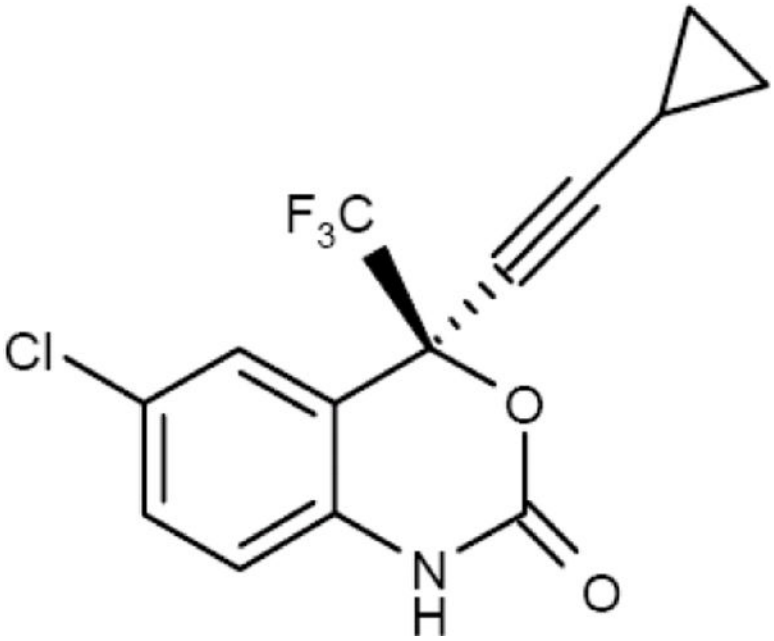

Figure 1.
The chemical structure of efavirenz.

Table 1

Patients with Adverse Events of Moderate or Severe Intensity Reported

	Squires[25,a]		5142[40, 41,b]		Markowitz[43,a]		Merit[44,a]	
Adverse Event	**EFV ZDV/3TC (N=401)**	**ATV ZDV/3TC (N=404)**	**EFV 2 NRTI (N=250)**	**LPV 2 NRTI (N=253)**	**EFV TDF/3TC (N=38)**	**RLT TDF/3TC (N=160)**	**EFV ZDV/3TC (N=361)**	**MVC ZDV/3TC (N=360)**
Clinical Adverse Event Grade ≥ 2, n (%)								
Headache	25 (6)	23 (6)	N/A	N/A	9 (24)	14 (9)	(~ 25)	(~ 25)
Dizziness	24 (6)	8 (2)[c]	N/A	N/A	11 (29)	14 (9)	(~ 30)	(~ 13)
Diarrhea	10 (2)	5 (1)	N/A	N/A	4 (11)	10 (6)	(~ 23)	(~ 18)
Vomiting	27 (7)	17 (4)	N/A	N/A	N/A	N/A	(~ 15)	(~ 12)
Nausea	51 (13)	57 (14)	N/A	N/A	5 (13)	18 (11)	(~ 33)	(~ 35)
Laboratory Adverse Event								
AST Grade ≥3, n (%)	8 (2)	7 (2)	(4)	(4)	N/A	N/A	11 (3.2)	12 (3.4)
ALT Grade ≥3, n (%)	10 (3)	15 (4)	(3)	(5)	2 (5)	6 (4)	11 (3.2)	11 (3.1)
Mean change in cholesterol, mg/dL (%)	(+21)	(+2)[c]	+33	+33[d]	~20	~0	+27	+1[c,d]
Mean change in triglycerides, mg/dL (%)	(+23)	(−9)[c]	14	44[d]	~50	~0	+10	−4[c,d]

ATZ: atazanavir; EFV: efavirenz; LPV/r: lopinavir/ritonavir; NRTI; nucleoside reverse transcriptase inhibitor; TDF: tenofovir disoproxil fumarate; RLT: raltegravir; ZDV: zidovudine; 3TC; lamivudine

[a] Week 48 results

[b] Week 96 results

[c] P<0.05

[d] median values

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Table 2

Viral and Immunologic Efficacy

Study	Drug dose (mg)	Drug dose (mg)	Other agents	Study period (weeks)	Number of subjects	Baseline HIV RNA, median (log10 copies/ml)	Percent undetectable at last visit [HIV RNA < 400 (50)]	CD4 increase, mean (cells/mm^3)
Squires[25, a]	EFV qd (600)	—	ZDV/3TC	48	401	4.91	64 (37)	160[b]
	—	ATV qd (400)	ZDV/3TC	48	404	4.87	70 (32)	176
5142[40,c]	EFV qd (600)	—	3TC/NRTI	96	250	5	76 (89)[b]	241[b,d]
	—	LPV/r bid (400/100)	3TC/NRTI	96	253	5	67 (77)	285
Markowitz[43,a]	EFV qd (600)	—	TDF/3TC	48	38	4.8[e]	87 (87)	170
	—	RLT bid (100 to 600)	TDF/3TC	48	160	4.6 - 4.8[c]	85-98 (83-88)	144-221
Merit[44]	EFV qd (600)	—	ZDV/3TC	48	361	4.88	73.1 (69.3)[b]	142[b]
	—	MVC bid (300)	ZDV/3TC	48	360	4.86	70.6 (65.3)	169

ATZ: atazanavir; EFV: efavirenz; LPV/r: lopinavir/ritonavir; NRTI; nucleoside reverse transcriptase inhibitor; TDF: tenofovir disoproxil fumarate; RLT: raltegravir; ZDV: zidovudine; 3TC; lamivudine

[a] For the intent-to-treat analysis in this study, missing values were treated as failures

[b] P<0.05 compared to comparator arm

[c] For the intent-to-treat analysis in this study, missing values were ignored

[d] median values

[e] mean values

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