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Efavirenz in the Therapy of HIV Infection

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Abstract

Importance of the field—The use of the first generation non-nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz (EFV) as a component of first-line antiretroviral therapy has been accepted worldwide. EFV is the only antiretroviral agent currently on the market that has been combined with emtricitabine and tenofovir disoproxil fumarate in a single tablet and administered once-daily.

Areas covered in this review—This article reviews efficacy and safety data on efavirenz and the role of pharmacogenetics in EFV exposure. Published articles and conference presentations on efavirenz are reviewed.

What the reader will gain—CYP2B6 genetic polymorphisms influence the metabolism of EFV. The CYP2B6 G to T polymorphism at position 516 has been shown to be associated with elevated plasma concentrations and an increase in neurotoxicity of EFV, while the wild-type genotype has been associated with sub-therapeutic concentrations of EFV, potentially leading to the development of viral resistance. This polymorphism is significantly higher in Sub-Saharan Africans and African Americans as compared to Hispanic, European and Asian populations.

Take home message—The significance of CYP2B6 polymorphism in EFV exposure indicates the need for prospective clinical studies to evaluate the utility of genotype-driven dose adjustments in populations of diverse descent.

Keywords

Antiretroviral Therapy; Efavirenz; Human Immunodeficiency Virus; Non-nucleoside Reverse Transcriptase Inhibitor; Pharmacogenetics

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Declaration of Interest

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1. Introduction

By the end of 2007 WHO estimated that 33 million people in the world were living with HIV. (1) Access to antiretroviral therapy (ART) in low and middle-income countries has been increasing at an accelerating pace. An estimated 4 million people in low- and middle-income countries were receiving ART at the end of 2008, compared to 3 million in 2007 and 400 000 in 2003.(2) The greatest increase in the number of people receiving ART was in sub-Saharan Africa. Efavirenz (EFV) (Box 1) is a first generation non-nucleoside reverse transcriptase inhibitor of HIV-1 and is one of the preferred component of the first line treatment regimen of HIV infection worldwide.(3,4) Taking into consideration the increasing access to ART, the potential for EFV exposure in world population is very large.(5)

Six classes of antiretroviral (ARV) agents are available for combination highly active antiretroviral (HAART) regimens: the nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors (FIs), CCR5 antagonists, and integrase inhibitors. Currently, preferred regimens use combinations of two NRTIs and either an NNRTI or a ritonavir-boosted PI. Both NNRTI-and PI-based regimens result in suppression of HIV RNA levels and CD4 T-cell increases in a large majority of patients. (6–10) Drug resistance to most PIs requires multiple mutations in the HIV protease, and it seldom develops after early virologic failure, especially with ritonavir boosting.(11) Resistance to the first generations NNRTIs, however, is conferred by a single mutation in reverse transcriptase, and develops rapidly after virologic failure.(11) PI-based regimens generally are associated with more gastrointestinal symptoms and lipid abnormalities, whereas NNRTI-based regimens are associated with more rash and central nervous system adverse effects.(8,9,12–14) From adherence perspective, NNRTI-based regimens are among the simplest to take, particularly with the co-formulated tablet of tenofovir disoproxil fumarate, emtricitabine, and EFV, which allows for once-daily dosing with a single tablet. All preferred PI-based may be dosed once or twice daily, and generally require more pills in the regimen. Drug-drug interactions are important with both types of regimens, but more clinically significant interactions are seen with PI-based regimens.

Second-generation NNRTI ((FDA approved etravirine (Intelence™, TMC125) and investigational Rilpivirine (TMC278)) exhibit activity against many viruses resistant to first-generation NNRTI and require multiple mutations for the development of the resistance.(15) Yet, the presence of some NNRTI mutations has been reported to reduce the treatment response. (16) Finally, limited studies have evaluated the use of FIs, CCR5 antagonists, and integrase inhibitors in large, randomized trials in treatment-naïve participants, and FI raltegravir is the only novel antiretroviral agent currently recommended as part of initial HAART in the US and EU.

EFV was approved by the FDA under accelerated review process on September 17, 1998, for use in combination with other ARV agents for the treatment of HIV-1 infection.(17) On the basis of clinical trial results and safety data, EFV is considered the preferred NNRTI as part of initial HAART except for pregnant women (especially during the first trimester) or in women of childbearing potential who are planning to conceive or who are sexually active with men without using effective and consistent contraception. In addition, EFV is used with other ARV agents as part of an expanded post exposure prophylaxis regimen to prevent HIV transmission in health care workers and other individuals with non-occupational exposure to HIV.

2. Chemistry and formulations

EFV is described as benzoxazinone derivative (2H-3,1-Benzoxazin-2-one,6-chloro-4-(cyclopropylethynyl)-1,4- dihydro-4-(trifluoromethyl)-,(4S)).(18) Its empirical formula is C₁₄H₉ClF₃NO₂ and its structural formula is shown in the Figure 1.(19) EFV is a white to

slightly pink crystalline powder with molecular weight of 315.68. The compound is practically insoluble in water (<10 mcg/ml). (18)

In the US EFV is manufactured as Sustiva® in capsules containing 50 mg and 200 mg of EFV and film-coated tablets containing 600 mg of EFV. It is also available in single pill once a day ART regimen in form of co-formulated tablet with 200 mg of Emtricitabine and 300 mg Tenofovir disoproxil fumarate (Atripla™). (18) In addition, several generic formulations of EFV have recently been approved by FDA through expedited review process in association with the President's Emergency Plan for AIDS Relief for the use in resource limited settings. (20)

3. Pharmacokinetics and metabolism

3.1 Pharmacokinetic studies in adult and pediatric patients

The time-to-peak plasma concentrations is approximately 3–5 hours and steady state C_{max} was mean (± SD) 12.9 ± μM. (18) EFV is readily absorbed and achieves peak serum concentration (C_{max}) of 4.07 mcg/ml 3–5 hours following 600 mg standard adult oral dose. (18) Increases in C_{max} and area under the plasma concentration-time curve (AUC) are dose proportional for 200, 400, and 600 mg EFV doses. The increases are less than proportional for a 1,600 mg EFV dose, suggesting reduced absorption at higher doses. EFV has a long serum half-life of 45 hours and reaches steady-state plasma concentrations in 6 to 10 days. The bioavailability of EFV is increased by reduced-fat/normal-caloric meal (EFV capsules) and particularly by high-fat/high-caloric meal (capsules and tablets) when compared to fasting. (18). The drug is highly protein bound (>99%), predominantly to albumin, and has a low CNS to plasma ratio for total drug, but 3-fold higher ratio for the unbound (free) EFV when compared to plasma. (18) The safety and efficacy of EFV in children less than 3 years of age has not been established. (21–25) The data on the EFV exposure in mothers and their breastfed infants is limited. (26) Despite the fact that EFV has been shown to be highly effective and well tolerated in the majority of pediatric patients (23,27), EFV plasma concentrations have been reported to be suboptimal in a large proportion (up to 57%) of children and adolescents dosed according to current pediatric guidelines. (21,22,28) The most recent data on population pharmacokinetics (PK) of EFV in children predicts sub-therapeutic EFV exposure in a significant proportion on children with the currently recommended EFV dose. (29,30) To date, no studies have investigated the impact of somatic growth and sexual maturation during puberty on EFV disposition.

Approximately 14–34% of a radiolabeled dose of EFV is recovered in the urine (less than 1% as unchanged drug) and 16–61% of a radiolabeled dose was recovered in feces (primarily as unchanged drug). (18) PK of EFV has not been studied in renal insufficiency. Since <1% of a dose is excreted unchanged in the urine, the impact of renal impairment on EFV elimination should be minimal. Safety and efficacy of EFV has not been established in patients with significant underlying liver disorders.

3.2 CYP2B6 metabolism of EFV

EFV is extensively metabolized primarily by hepatic CYP2B6 with partial involvement of CYP3A4 and CYP2A6 to inactive hydroxylated metabolites that include 8-hydroxy and 7-hydroxyefavirenz. (31–34) The 8-hydroxyefavirenz is the major metabolite of EFV in vitro and in vivo, and the contribution of 7-hydroxylation to the overall clearance of EFV is considered to be small. (33) Recent studies suggest that CYP2A6 is primarily responsible for 7-hydroxylation. (35) CYP2B6 further catalyzes second step of hydroxylation of the 8-hydroxymetabolite to 8,14-dihydroxyefavirenz and it is estimated that ~17% of 8-hydroxyefavirenz is further oxidized to 8,14-dihydroxyefavirenz in vitro. (31,33) Hydroxylated

EFV metabolites undergo subsequent urinary and biliary excretion after conjugation (mainly glucuronidation). 8-hydroxyefavirenz is responsible for false-positive urine benzodiazepine and cannabinoid tests in patients receiving EFV.(36)

In vitro studies have shown that CYP2B6 genetic polymorphisms markedly influence the metabolism of EFV.(32–34) The CYP2B6*6 allele harboring two SNPs (516G>T and 785A>G) was significantly associated with a pronounced decrease in CYP2B6 expression and a low rate of 8-hydroxylation of EFV. The data from in vitro studies suggest that 8-hydroxylation of EFV is a specific marker of CYP2B6 activity and can be used as a phenotyping probe to evaluate expression of CYP2B6 in humans, and the choice of this probe is supported by the FDA guidelines on genomic studies. (33,34)

CYP2B6 polymorphisms have been associated with altered PK of EFV in HIV-infected adults.(37–40) The CYP2B6 G to T polymorphism at position 516 has been strongly associated with elevated EFV plasma concentrations and an increase in neurotoxicity (32,41), while up to 20% of subjects with wild-type genotype have been reported to have sub-therapeutic EFV concentrations (42). The CYP2B6 G516T polymorphism has also been associated with a prolonged elimination serum half-life and an increased risk of developing drug resistance after discontinuation of EFV-based regimen.(43) Most recently the CYP2B6 983T>C and CYP2A6 (CYP2A6*9B and CYP2A6*17) genotypes has also been reported to affect EFV plasma concentrations.(44–46) Individuals with a poor metabolizer genotype had a likelihood ratio of 35 (95% CI, 11–110) of very high EFV plasma levels.(45) These data have demonstrated that CYP2B6 poor metabolizer genotypes can identify individuals at risk of high EFV plasma concentrations. High EFV plasma concentrations and successful genotype-based EFV dose reduction were further demonstrated in individuals with the haplotypes CYP2B6 *6/*6 (516G>T, 785A>G) and *6/*26 (499C>G, 516G>T, 785A>G).(47) Most recently, genotype CYP2B6 based dose reduction has been proposed in several population PK models.(48,49)

Of great importance is the high prevalence of EFV related CYP2B6 polymorphisms in patients of African descent who currently represent the majority of the HIV-infected population worldwide.(40,43,44,50–54) The 516 T allelic frequency is significantly higher in Sub-Saharan Africans (45.5%) and African Americans (46.7%) as compared to Hispanic (27.3%), European (21.4%) and Asian (17.4%) populations, indicating the need for prospective clinical dose optimization studies to evaluate the utility of genotype-driven dose adjustments in diverse populations.(37,51,55) Simulations indicate that an a priori 35% EFV dose reduction in homozygous CYP2B6*6 patients would maintain drug exposure within the therapeutic range in African patients.(51)

CYP2B6 G516T polymorphisms were also shown to affect the clearance of EFV in children.(24,56) The possibility of changes in hepatic enzyme activity by age may need to be considered when evaluating the impact of genetic variants on EFV PK in children. To date the data on the effects of CYP2B6 polymorphisms on the clinical outcome has been limited (52) and questions regarding the impact of this polymorphism on the long-term virological and immunological response to EFV therapy remains to be answered.

3.3 Drug and Food Interactions

EFV has been shown to be a substrate and inhibitor and inducer of several P450 enzymes (CYP2B6, CYP3A4, CYP2A6, CYP2C9 and CYP2C19), resulting in the induction of its own metabolism and multiple drug-drug interactions. Drugs and substances that induce these isoenzymes may reduce EFV plasma concentrations, while co-administration of EFV with drugs primarily metabolized by CYP3A4 may result in altered plasma concentrations of those drugs. Cisapride, ergot alkaloids and derivatives, midazolam, or triazolam, bepridil, pimozone, and St.John's wort are not recommended to be used concomitantly with EFV. (18,57)

Clinically important interactions occur when EFV is used in conjunction with PIs. Plasma concentrations of atazanavir, amprenavir/fosamprenavir, indinavir, lopinavir (in fixed dose combination with ritonavir), nelfinavir, and saquinavir are decreased, and require dose adjustment for certain PIs (atazanavir/lopinavir/ritonavir, indinavir), boosted ritonavir for others (atazanavir, fosamprenavir) and close monitoring for the rest of PIs except for tipranavir. (18,58–61) PK studies evaluating concomitant use of EFV and the other NNRTIs have not been performed and clinically important PK interactions are not expected between EFV and NRTIs.

Concurrent use of rifampicin decreases EFV plasma concentrations in adults(62), while co-administration with use of rifabutin does not affect EFV plasma concentrations but decreases rifabutin plasma concentrations(63). EFV may decrease the plasma concentration of clarithromycin, however co-administration with azithromycin did not result in clinically significant PK changes. Concurrent administration with voriconazole produces decrease in voriconazole exposure and increases EFV AUC requiring dose adjustment for both agents. (64)

Co-administration of methadone and EFV significantly decreases the C_{max} and AUC of methadone and may result in manifestations of opiate withdrawal requiring the increase of maintenance methadone dose.(65) The concentrations of anticonvulsant agents (carbamazepine, phenobarbital, phenytoin) have been reported to be altered by EFV.(66)

Studies have demonstrated significant decreases in the progestin component of the oral contraceptives and no changes in the EFV or estrogen component.(61) Since the clinical significance of this elevation is unknown, the addition of a reliable method of barrier contraception is recommended for all female patients taking EFV.(67) EFV interactions with St. John's wort (*Hypericum perforatum*) or St. John's wort-containing products need also to be taken into consideration as St. John's wort has been reported to substantially decrease EFV plasma concentrations. (18)

4. Pharmacodynamics

EFV is a noncompetitive inhibitor of HIV-1 reverse transcriptase (RT). It has no inhibitory effect on HIV-2 RT or human cellular DNA polymerases alpha, beta, gamma, or delta.(18) EFV binds directly to RT and inhibits viral RNA- and DNA-dependent DNA polymerase activities by disrupting the catalytic site. Although the drug-RT-template complex may continue to bind deoxynucleoside triphosphate and to catalyze its incorporation into the newly forming viral DNA, it does so at a slower rate. Large randomized, controlled trials and cohort studies of treatment-naïve patients have demonstrated potent viral suppression in EFV treated patients: a substantial proportion of patients had HIV RNA <50 copies/mL up to 7 years of follow-up.(6,7,68,69) Studies that compared EFV-based regimens with other regimens have demonstrated that regimens that contained EFV with two NRTIs were superior virologically to some PI-based regimens, including indinavir(8), lopinavir/ritonavir (10), and nelfinavir (70), and to triple-NRTI-based regimens(71,72). EFV-based regimens had comparable activities to nevirapine- (12,14) and atazanavir-based regimens (9). The ACTG 5142 study randomized patients to receive two NRTIs together with either EFV or lopinavir/ritonavir (or an NRTI-sparing regimen of EFV and lopinavir/ritonavir).(10) The dual-NRTI and EFV regimen was associated with a significantly better virologic response than the dual NRTI and lopinavir/ritonavir regimen at 96 weeks, whereas the dual-NRTI with lopinavir/ritonavir regimen was associated with a significantly better CD4 cell response and less drug resistance after virologic failure.

To date no evidence has demonstrated that new ART classes such as CCR5 antagonists, integrase inhibitors or second-generation NNRTIs are more effective than EFV in treatment-

naïve patients with several studies are in progress. A recent data from the MERIT study comparing CCR5 inhibitor maraviroc with EFV found that maraviroc was non-inferior to EFV when 15% of patient with mixed tropism were excluded using a more sensitive TrofileTM assay. (73) Integrase inhibitor raltegravir was compared to EFV in two studies. (74,75) The 004 and STARTMRK studies demonstrated similar rates of virologic suppression and increase in CD4 cell count for raltegravir and EFV with better tolerance of integrase inhibitor. Studies on the comparison of the second-generation NNRTIs with EFV in treatment-naïve patients are in progress.

Although the mechanism of viral resistance or reduced susceptibility to EFV has not been fully determined, the principal mechanism of resistance appears to be mutation of HIV RT. Like the other NNRTIs, EFV has a low genetic barrier to resistance and selects for mutations that usually involve the regions of HIV RT that include amino acid positions 98 through 108 and 179 through 190, although mutations at position 225 have also been reported. (11) High-level resistance is seen with a single mutation (typically RT gene codon 103) as a result of sub-therapeutic drug exposure. Long term suppression of HIV replication has been associated with maintenance of trough EFV concentrations >1 mcg/mL in adults and children, while trough concentrations exceeding 4 mcg/mL have been proven to increase the risk of adverse central nervous system (CNS) effects potentially leading to discontinuation of ART. (22,25,76)

The potential for cross resistance between EFV and nucleoside reverse transcriptase inhibitors (NRTIs) is considered low because the drugs bind at different sites and have different mechanisms of action. Cross resistance between EFV and HIV protease inhibitors (PIs) is unlikely because of the different enzyme targets involved.

5. Safety and Tolerability

EFV is FDA Pregnancy Category D and its use is not recommended during the first trimester of pregnancy or in women with high pregnancy potential due to the concern for teratogenicity. (18) In prospective reports, birth defects have occurred in 13 of 407 live births with first-trimester EFV exposure and in 2 of 37 live births with second/third-trimester exposures. Birth defects included neural tube defects including meningocele, and anophthalmia in combination with severe oblique facial clefts and amniotic banding. (57,77,78) Similar defects have been observed in preclinical studies. Two methods of birth control, with a barrier method in combination with a non-barrier method (hormonal contraceptive), should be used with EFV-based ART and for 12 weeks after discontinuation of the drug. (67) Pregnancy test is recommended in all women of childbearing age prior to initiation of EFV-based ART. The administration to EFV to women of childbearing age requires availability and cultural acceptance of effective contraception.

EFV has a high rate of CNS side effects (up to 55%) including more frequently dizziness, insomnia, impaired concentration, agitation, amnesia, somnolence, abnormal dreams and hallucinations. (18) These symptoms usually begin during the first days of therapy and generally resolve after 2–4 weeks with up to 10% of patients with persistent complaints discontinuing the drug. (18) CNS toxicity has been reported more frequently in adult and pediatric patients with high EFV trough plasma concentrations > 4 mcg/mL. (76) Other CNS manifestations include depression, anxiety, and nervousness, and occasional post-marketing reports of death by suicide or psychosis-like behavior in patients taking EFV have been made. (18) False-positive urine cannabinoid test results have been observed in non-HIV-infected volunteers receiving EFV when the Microgenics CEDIA DAU Multi-Level THC assay was used for screening. Negative results were obtained with other assay and with more specific confirmatory testing. (18)

Skin rashes usually appear as mild or moderate maculopapular eruptions that occur within the first 2 weeks of therapy and in most patients resolve within 1 month with continuing EFV administration. Children have a higher incidence of rash (46% of children compared to 26% of adults).(18,79) Erythema multiforme and Stevens-Johnson syndrome are extremely rare (0.1%) in adults and more frequent in children (5%), and require discontinuation of EFV. Gastrointestinal effects (nausea, diarrhea, vomiting, anorexia and malabsorption) have been reported in up to 14% of adults receiving EFV. Significant elevation of liver enzymes and hepatic failure can be present with or without co-infection with hepatitis B or C. While the patients on EFV-based ART show fewer atherogenic lipid changes than patients treated with PI-based regimen(80,81), EFV may increase the concentration of total cholesterol and triglycerides.(13,18) Lipodystrophy, moderate or severe pain, abnormal vision, arthralgia, asthenia, dyspnea, gynecomastia, myalgia, myopathy, and tinnitus have also been reported. (18)

6. Conclusion

Antiretroviral activity of EFV has been proven to be equivalent or superior to all comparators to date. EFV based ART carries a low pill burden and is administered once a day due to a long half-life. EFV is currently the only antiretroviral agent available in a fixed-dose combination with two NRTIs in single pill administered once-daily as a complete HAART, which has the potential of preserving high adherence rates necessary to achieve sustained virologic suppression. Once-daily EFV based ART has been demonstrated to be a safe, convenient and potent antiretroviral regimen in HIV-1 infected adults, children and adolescents. (82,83) Due to the well defined therapeutic index EFV is suitable for the successful application of therapeutic drug monitoring in management of ART.

7. Expert Opinion

Despite emergence of second-generation NNRTIs and new classes of antiretroviral agents such as integrase inhibitors and CCR5 inhibitors, EFV retains his role as the preferred NNRTI for the initial antiretroviral therapy worldwide based on the regimen feasibility and cost considerations. The significance of CYP2B6 polymorphism in EFV exposure, particularly in the patients of African origin, indicates the need for prospective clinical studies to evaluate the utility of genotype-driven dose adjustments in populations of diverse descent. Studies are required to access the developmental changes of EFV in children and adolescents and to evaluate the EFV exposure in the newborns exposed to EFV administered to the mothers.

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REFERENCES

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. UNAIDS. AIDS epidemic update : December 2007. [Accessed June 11, 2009]. Available at: http://data.unaids.org/pub/EPISlides/2007/2007_epiupdate_en.pdf
2. WHO, UNAIDS, UNICEF. Scaling up access to antiretroviral therapy to low- and midlde-income countries: global and regional progress in 2008. [Accessed August 31 2009]. Availabe at: http://www.who.int/hiv/mediacentre/ias_2009pdf

3. Department of Health and Human Services. Panel on Antiretroviral Guidelines for Adult and Adolescents; Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. 2008 Jan 29 [Accessed March 27, 2008]. p. 1-128. Available at: <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>
4. Antiretroviral therapy for HIV infection in adults and adolescents. Recommendations for a public health approach RW. 2006 [Accessed March 27, 2008]. Available at: <http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf>
5. UNAIDS. AIDS epidemic update : December 2007. [Accessed April 1, 2008.2007]. Available at http://data.unaids.org/pub/EPISlides/2007/2007_epiupdate_en.pdf
6. Gulick RM, Ribaudo HJ, Shikuma CM, et al. Three- vs four-drug antiretroviral regimens for the initial treatment of HIV-1 infection: a randomized controlled trial. JAMA 2006 Aug 16;296(7):769–781. [PubMed: 16905783] ** Important trial comparing 3-drug and 4-drug antiretroviral regimes with efavirenz in treatment naive patients.
7. Gallant JE, Staszewski S, Pozniak AL, et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naïve patients: a 3-year randomized trial. JAMA 2004 Jul 14;292(2):191–201. [PubMed: 15249568]
8. Staszewski S, Morales-Ramirez J, Tashima KT, et al. Study 006 Team. Efavirenz plus zidovudine and lamivudine, efavirenz plus didanosine, and didanosine plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. N Engl J Med 1999 Dec 16;341(25):1865–1873. [PubMed: 10601505]
9. Squires K, Lazzarin A, Gatell JM, et al. Comparison of once-daily atazanavir with efavirenz, each in combination with fixed-dose zidovudine and lamivudine, as initial therapy for patients infected with HIV. J Acquir Immune Defic Syndr 2004 Aug 15;36(5):1011–1019. [PubMed: 15247553] * Important trial on initial HIV treatment comparing once-daily atazanavir with efavirenz based HAART regimens.
10. Riddler SA, Haubrich R, DiRienzo AG, et al. Class-sparing regimens for initial treatment of HIV-1 infection. N Engl J Med 2008 May 15;358(20):2095–2106. [PubMed: 18480202] ** Important study on class-sparing regimen with efaviran or lopinavir-ritonavir with two nucleoside reverse-transcriptase inhibitors and lopinavir-ritonavir with efavirenz (NRTI-sparing).
11. Hirsch MS, Gunthard HF, Schapiro JM, et al. Antiretroviral drug resistance testing in adult HIV-1 infection: 2008 recommendations of an International AIDS Society-USA panel. Clin Infect Dis 2008 Jul 15;47(2):266–285. [PubMed: 18549313]
12. van Leth F, Phanuphak P, Ruxrungtham K, et al. Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study. Lancet 2004 Apr 17;363(9417):1253–1263. [PubMed: 15094269]
13. Haubrich RH, Riddler SA, DiRienzo AG, et al. Metabolic outcomes in a randomized trial of nucleoside, nonnucleoside and protease inhibitor-sparing regimens for initial HIV treatment. AIDS 2009 Jun 1;23(9):1109–1118. [PubMed: 19417580] * Valuable data comparing the lipoatrophy and lipid changes associated with different initial HAART regimens.
14. Nunez M, Soriano V, Martin-Carbonero L, et al. SENC (Spanish efavirenz vs. nevirapine comparison) trial: a randomized, open-label study in HIV-infected naïve individuals. HIV Clin Trials 2002 May–Jun;3(3):186–194. [PubMed: 12032877]
15. Ghosn J, Chaix ML, Delaugerre C. HIV-1 resistance to first- and second-generation non-nucleoside reverse transcriptase inhibitors. AIDS Rev 2009 Jul–Sep;11(3):165–173. [PubMed: 19654858]
16. Scherrer AU, Hasse B, von Wyl V, et al. Prevalence of etravirine mutations and impact on response to treatment in routine clinical care: the Swiss HIV Cohort Study (SHCS). HIV Med. 2009 Sep 1;
17. FDA - Approval Letter. [Accessed July 12 2009]. Available at: <http://www.fda.gov/cder/foi/applletter/1998/20972ltr.pdf>
18. Sustiva® Prescribing Information. Bristol-Myers Squibb Company. 2009 March;
19. ChemIDplus Advanced. [Accessed July 12 2009]. Available at: <http://chem.sis.nlm.nih.gov/chemidplus/chemidheavy.jsp>
20. FDA, U.S. Department of Health and Human Services. FDA Antiretrovirals Approved and Tentatively Approved in Association with the President's Emergency Plan Expedited Review Process. [Accessed August 12, 2009]. Available at: <http://www.fda.gov/InternationalPrograms/FDABeyondOurBordersForeignOffices/AsiaandAfrica/ucm119231.htm>

21. von Hentig N, Koenigs C, Elanjikal S, et al. Need for therapeutic drug monitoring in HIV-1 infected children receiving efavirenz doses according to international guidelines. *Eur J Med Res* 2006 Sep 29;11(9):377–380. [PubMed: 17101460]
22. Ren Y, Nuttall JJ, Egbers C, et al. High prevalence of subtherapeutic plasma concentrations of efavirenz in children. *J Acquir Immune Defic Syndr* 2007 Jun 1;45(2):133–136. [PubMed: 17417100]
23. Wintergerst U, Hoffmann F, Jansson A, et al. Antiviral efficacy, tolerability and pharmacokinetics of efavirenz in an unselected cohort of HIV-infected children. *J Antimicrob Chemother.* 2008 Mar 13;
24. Saitoh A, Fletcher CV, Brundage R, et al. Efavirenz pharmacokinetics in HIV-1-infected children are associated with CYP2B6-G516T polymorphism. *J Acquir Immune Defic Syndr* 2007 Jul 1;45(3):280–285. [PubMed: 17356468]
25. Fletcher CV, Brundage RC, Fenton T, et al. Pharmacokinetics and pharmacodynamics of efavirenz and nelfinavir in HIV-infected children participating in an area-under-the-curve controlled trial. *Clin Pharmacol Ther* 2008 Feb;83(2):300–306. [PubMed: 17609682]
26. Schneider S, Peltier A, Gras A, et al. Efavirenz in human breast milk, mothers', and newborns' plasma. *J Acquir Immune Defic Syndr* 2008 Aug 1;48(4):450–454. [PubMed: 18614925] *Valuable report of the pharmacokinetics of efavirenz in newborn infants and breast milk.
27. Teglas JP, Quartier P, Treluyer JM, et al. Tolerance of efavirenz in children. *AIDS* 2001 Jan 26;15(2):241–243. [PubMed: 11216933]
28. Starr SE, Fletcher CV, Spector SA, et al. Efavirenz liquid formulation in human immunodeficiency virus-infected children. *Pediatr Infect Dis J* 2002 Jul;21(7):659–663. [PubMed: 12237599]
29. ter Heine, R.; Scherpier, H.; Crommentuyn, K., et al. Population pharmacokinetics in children. Current pediatric dosing guidelines may result in sub-therapeutic concentrations; Annual meeting of American Society of Clinical Pharmacology and Therapeutics (ASCPT); Orlando, FL. 2008.
30. Hirt D, Urien S, Olivier M, et al. Are recommended dose of efavirenz optimal in young West African HIV-infected children? (ANRS 12103). *Antimicrob Agents Chemother.* 2009 Jul 27; *Important report on suboptimal efavirenz exposure in African children.
31. Mutlib AE, Chen H, Nemeth GA, et al. Identification and characterization of efavirenz metabolites by liquid chromatography/mass spectrometry and high field NMR: species differences in the metabolism of efavirenz. *Drug Metab Dispos* 1999 Nov;27(11):1319–1333. [PubMed: 10534318]
32. Desta Z, Saussele T, Ward B, et al. Impact of CYP2B6 polymorphism on hepatic efavirenz metabolism in vitro. *Pharmacogenomics* 2007 Jun;8(6):547–558. [PubMed: 17559344] ** Important in vitro study that shows the role of CYP2B6 genetic polymorphism in the metabolism of efavirenz in human liver microsomes.
33. Ward BA, Gorski JC, Jones DR, et al. The cytochrome P450 2B6 (CYP2B6) is the main catalyst of efavirenz primary and secondary metabolism: implication for HIV/AIDS therapy and utility of efavirenz as a substrate marker of CYP2B6 catalytic activity. *J Pharmacol Exp Ther* 2003 Jul;306(1):287–300. [PubMed: 12676886]
34. Bumpus NN, Kent UM, Hollenberg PF. Metabolism of efavirenz and 8-hydroxyefavirenz by P450 2B6 leads to inactivation by two distinct mechanisms. *J Pharmacol Exp Ther* 2006 Jul;318(1):345–351. [PubMed: 16611850]
35. di Iulio J, Fayet A, Arab-Alameddine M, et al. In vivo analysis of efavirenz metabolism in individuals with impaired CYP2A6 function. *Pharmacogenet Genomics* 2009 Apr;19(4):300–309. [PubMed: 19238117]
36. Blank A, Hellstern V, Schuster D, et al. Efavirenz treatment and false-positive results in benzodiazepine screening tests. *Clin Infect Dis* 2009 Jun 15;48(12):1787–1789. [PubMed: 19432553]
37. Lang T, Klein K, Richter T, et al. Multiple novel nonsynonymous CYP2B6 gene polymorphisms in Caucasians: demonstration of phenotypic null alleles. *J Pharmacol Exp Ther* 2004 Oct;311(1):34–43. [PubMed: 15190123]
38. Rotger M, Colombo S, Furrer H, et al. Influence of CYP2B6 polymorphism on plasma and intracellular concentrations and toxicity of efavirenz and nevirapine in HIV-infected patients. *Pharmacogenet Genomics* 2005 Jan;15(1):1–5. [PubMed: 15864119]

39. Tsuchiya K, Gatanaga H, Tachikawa N, et al. Homozygous CYP2B6 *6 (Q172H and K262R) correlates with high plasma efavirenz concentrations in HIV-1 patients treated with standard efavirenz-containing regimens. *Biochem Biophys Res Commun* 2004 Jul 9;319(4):1322–1326. [PubMed: 15194512]
40. Klein K, Lang T, Saussele T, et al. Genetic variability of CYP2B6 in populations of African and Asian origin: allele frequencies, novel functional variants, and possible implications for anti-HIV therapy with efavirenz. *Pharmacogenet Genomics* 2005 Dec;15(12):861–873. [PubMed: 16272958]
41. Haas DW, Ribaud HJ, Kim RB, et al. Pharmacogenetics of efavirenz and central nervous system side effects: an Adult AIDS Clinical Trials Group study. *AIDS* 2004 Dec 3;18(18):2391–2400. [PubMed: 15622315] *Important information on the association of the CYP2B6 genotype and central nervous system side effects of efavirenz therapy.
42. Rodriguez-Novoa S, Barreiro P, Rendon A, et al. Influence of 516G>T polymorphisms at the gene encoding the CYP450-2B6 isoenzyme on efavirenz plasma concentrations in HIV-infected subjects. *Clin Infect Dis* 2005 May 1;40(9):1358–1361. [PubMed: 15825040]
43. Ribaud HJ, Haas DW, Tierney C, et al. Pharmacogenetics of plasma efavirenz exposure after treatment discontinuation: an Adult AIDS Clinical Trials Group Study. *Clin Infect Dis* 2006 Feb 1;42(3):401–407. [PubMed: 16392089]
44. Wyen C, Hendra H, Vogel M, et al. Impact of CYP2B6 983T>C polymorphism on non-nucleoside reverse transcriptase inhibitor plasma concentrations in HIV-infected patients. *J Antimicrob Chemother* 2008 Apr;61(4):914–918. [PubMed: 18281305]
45. Rotger M, Tegude H, Colombo S, et al. Predictive value of known and novel alleles of CYP2B6 for efavirenz plasma concentrations in HIV-infected individuals. *Clin Pharmacol Ther* 2007 Apr;81(4):557–566. [PubMed: 17235330]
46. Kwara A, Lartey M, Sagoe KW, et al. CYP2B6 (c.516G-->T) and CYP2A6 (*9B and/or *17) polymorphisms are independent predictors of efavirenz plasma concentrations in HIV-infected patients. *Br J Clin Pharmacol* 2009 Apr;67(4):427–436. [PubMed: 19371316]
47. Gatanaga H, Hayashida T, Tsuchiya K, et al. Successful efavirenz dose reduction in HIV type 1-infected individuals with cytochrome P450 2B6 *6 and *26. *Clin Infect Dis* 2007 Nov 1;45(9):1230–1237. [PubMed: 17918089]
48. Cabrera SE, Santos D, Valverde MP, et al. Influence of the cytochrome P450 2B6 genotype on population pharmacokinetics of efavirenz in human immunodeficiency virus patients. *Antimicrob Agents Chemother* 2009 Jul;53(7):2791–2798. [PubMed: 19433561]
49. Arab-Alameddine M, Di Iulio J, Buclin T, et al. Pharmacogenetics-based population pharmacokinetic analysis of efavirenz in HIV-1-infected individuals. *Clin Pharmacol Ther* 2009 May;85(5):485–494. [PubMed: 19225447] *Important study justifying the dosage adjustment in accordance with the type of polymorphism (CYP2B6, CYP2A6, or CYP3A4) in order to maintain the therapeutic target levels for efavirenz.
50. Wang J, Sonnerborg A, Rane A, et al. Identification of a novel specific CYP2B6 allele in Africans causing impaired metabolism of the HIV drug efavirenz. *Pharmacogenet Genomics* 2006 Mar;16(3):191–198. [PubMed: 16495778]
51. Nyakutira C, Roshammar D, Chigutsa E, et al. High prevalence of the CYP2B6 516G-->T(*6) variant and effect on the population pharmacokinetics of efavirenz in HIV/AIDS outpatients in Zimbabwe. *Eur J Clin Pharmacol* 2008 Apr;64(4):357–365. [PubMed: 18057928]
52. Haas DW, Smeaton LM, Shafer RW, et al. Pharmacogenetics of long-term responses to antiretroviral regimens containing Efavirenz and/or Nelfinavir: an Adult AIDS Clinical Trials Group Study. *J Infect Dis* 2005 Dec 1;192(11):1931–1942. [PubMed: 16267764]
53. Gross R, Aplenc R, Tenhave T, et al. Slow efavirenz metabolism genotype is common in Botswana. *J Acquir Immune Defic Syndr* 2008 Nov 1;49(3):336–337. [PubMed: 18978480]
54. Leger P, Dillingham R, Beauharnais CA, et al. CYP2B6 Variants and Plasma Efavirenz Concentrations during Antiretroviral Therapy in Port-au-Prince, Haiti. *J Infect Dis* 2009 Sep 15;200(6):955–964. [PubMed: 19659438]
55. Mehlotra RK, Ziats MN, Bockarie MJ, et al. Prevalence of CYP2B6 alleles in malaria-endemic populations of West Africa and Papua New Guinea. *Eur J Clin Pharmacol* 2006 Apr;62(4):267–275. [PubMed: 16506047]

56. Puthanakit T, Tanpaiboon P, Aupibul L, et al. Plasma efavirenz concentrations and the association with CYP2B6-516G>T polymorphism in HIV-infected Thai children. *Antivir Ther* 2009;14(3):315–320. [PubMed: 19474465]
57. Department of Health and Human Services. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. [Accessed August 12, 2009]. Updated November 3, 2008. Available at: <http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf>
58. Poirier JM, Guiard-Schmid JB, Meynard JL, et al. Critical drug interaction between ritonavir-boosted atazanavir regimen and non-nucleoside reverse transcriptase inhibitors. *AIDS* 2006 Apr 24;20(7):1087–1089. [PubMed: 16603872]
59. Sekar VJ, De Pauw M, Marien K, et al. Pharmacokinetic interaction between TMC114/r and efavirenz in healthy volunteers. *Antivir Ther* 2007;12(4):509–514. [PubMed: 17668559]
60. Hsu A, Isaacson J, Brun S, et al. Pharmacokinetic-pharmacodynamic analysis of lopinavir-ritonavir in combination with efavirenz and two nucleoside reverse transcriptase inhibitors in extensively pretreated human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother* 2003 Jan;47(1):350–359. [PubMed: 12499212]
61. Sustiva® Prescribing Information. Bristol-Myers Squibb Company. 2009 September;
62. Matteelli A, Regazzi M, Villani P, et al. Multiple-dose pharmacokinetics of efavirenz with and without the use of rifampicin in HIV-positive patients. *Curr HIV Res* 2007 May;5(3):349–353. [PubMed: 17504177]
63. Weiner M, Benator D, Peloquin CA, et al. Evaluation of the drug interaction between rifabutin and efavirenz in patients with HIV infection and tuberculosis. *Clin Infect Dis* 2005 Nov 1;41(9):1343–1349. [PubMed: 16206114]
64. Damle B, LaBadie R, Crownover P, et al. Pharmacokinetic interactions of efavirenz and voriconazole in healthy volunteers. *Br J Clin Pharmacol* 2008 Apr;65(4):523–530. [PubMed: 18294336]
65. Clarke SM, Mulcahy FM, Tjia J, et al. The pharmacokinetics of methadone in HIV-positive patients receiving the non-nucleoside reverse transcriptase inhibitor efavirenz. *Br J Clin Pharmacol* 2001 Mar; 51(3):213–217. [PubMed: 11298066]
66. Robertson SM, Penzak SR, Lane J, et al. A potentially significant interaction between efavirenz and phenytoin: a case report and review of the literature. *Clin Infect Dis* 2005 Jul 15;41(2):e15–e18. [PubMed: 15983905]
67. El-Ibiary SY, Cocohoba JM. Effects of HIV antiretrovirals on the pharmacokinetics of hormonal contraceptives. *Eur J Contracept Reprod Health Care* 2008 Jun;13(2):123–132. [PubMed: 18465473]
68. Novak RM, Chen L, MacArthur RD, et al. Prevalence of antiretroviral drug resistance mutations in chronically HIV-infected, treatment-naïve patients: implications for routine resistance screening before initiation of antiretroviral therapy. *Clin Infect Dis* 2005 Feb 1;40(3):468–474. [PubMed: 15668873]
69. Cassetti JM, Eitzel A. The safety and efficacy of tenofovir DF (TDF) in combination with lamivudine (3TC) and efavirenz (EFV) in antiretroviral-naïve patients through seven years. 17th International AIDS Conference August 3–8, 2008 Mexico City, Mexico Abstract TUPE0057 *Valuable data on the long term safety and efficacy of efavirenz based regimens.
70. Robbins GK, De Gruttola V, Shafer RW, et al. Comparison of sequential three-drug regimens as initial therapy for HIV-1 infection. *N Engl J Med* 2003 Dec 11;349(24):2293–2303. [PubMed: 14668455]
71. Gulick RM, Ribaud HJ, Shikuma CM, et al. Triple-nucleoside regimens versus efavirenz-containing regimens for the initial treatment of HIV-1 infection. *N Engl J Med* 2004 Apr 29;350(18):1850–1861. [PubMed: 15115831] **Important trial comparing triple-nucleoside regimens with efavirenz-based regimens in treatment naïve patients.
72. Gallant JE, Rodriguez AE, Weinberg WG, et al. Early virologic nonresponse to tenofovir, abacavir, and lamivudine in HIV-infected antiretroviral-naïve subjects. *J Infect Dis* 2005 Dec 1;192(11):1921–1930. [PubMed: 16267763]
73. Saag, MHJ.; Goodrich, J., et al. Reanalysis of the MERIT study with the enhanced Trofile™ assay. Abstracts of the Forty-eighth Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, DC, USA; American Society for Microbiology; Washington, DC, USA. 2008. Abstract H-1232

74. Markowitz M, Nguyen BY, Gotuzzo E, et al. Rapid and durable antiretroviral effect of the HIV-1 Integrase inhibitor raltegravir as part of combination therapy in treatment-naïve patients with HIV-1 infection: results of a 48-week controlled study. *J Acquir Immune Defic Syndr* 2007 Oct 1;46(2):125–133. [PubMed: 17721395]
75. Markowitz, MNB-Y.; Gotuzzo, E., et al. Sustained antiretroviral efficacy of raltegravir as part of combination ART in treatment-naïve HIV-1-infected patients: 96-week data. Abstracts of the Seventeenth International AIDS Conference; Mexico City, Mexico. 2008. Abstract TUAB0102
76. Marzolini C, Telenti A, Decosterd LA, et al. Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1-infected patients. *AIDS* 2001 Jan 5;15(1):71–75. [PubMed: 11192870]
77. Saitoh A, Hull AD, Franklin P, et al. Myelomeningocele in an infant with intrauterine exposure to efavirenz. *J Perinatol* 2005 Aug;25(8):555–556. [PubMed: 16047034]
78. Watts DH. Teratogenicity risk of antiretroviral therapy in pregnancy. *Curr HIV/AIDS Rep* 2007 Aug;4(3):135–140. [PubMed: 17883999]
79. Department of Health and Human Services. Guidelines for the use of antiretroviral agents in pediatric HIV infection. [Accessed June 27, 2009]. Updated February 23, 2009. Available at: <http://aidsinfo.nih.gov/contentfiles/PediatricGuidelines.pdf>
80. van Leth F, Phanuphak P, Stoes E, et al. Nevirapine and efavirenz elicit different changes in lipid profiles in antiretroviral-therapy-naïve patients infected with HIV-1. *PLoS Med* 2004 Oct;1(1):e19. [PubMed: 15526045]
81. McComsey G, Bhumbra N, Ma JF, et al. Impact of protease inhibitor substitution with efavirenz in HIV-infected children: results of the First Pediatric Switch Study. *Pediatrics* 2003 Mar;111(3):e275–e281. [PubMed: 12612284]
82. Scherpbier HJ, Bekker V, Pajkrt D, et al. Once-daily highly active antiretroviral therapy for HIV-infected children: safety and efficacy of an efavirenz-containing regimen. *Pediatrics* 2007 Mar;119(3):e705–e715. [PubMed: 17308244]
83. Rathore, M.; McKinney, R.; Hu, C., et al., editors. PACTG protocol 1021: a phase I/II study of a once-daily regimen of Emtricitabine, Didanosine, and Efavirenz in HIV-infected, therapy-naïve children and adolescents. Program and abstracts of the 15th Conference on Retroviruses and Opportunistic Infections; Boston, MA. 2008. Abstract 581

Figure 1.
Structural Formula of Efavirenz.(19)

Table 1

Drug name	Efavirenz
Phase	Launched
Indication	Infection, HIV/AIDS
Pharmacology description	RNA directed DNA polymerase inhibitor Non-nucleoside reverse transcriptase inhibitor
Route of administration	Alimentary, po
Chemical structure
Pivotal trial(s)	<p>In an open-label study, three regimens for initial HIV therapy were compared in an ACTG study A5142: efavirenz plus two NRTIs (efavirenz group), lopinavir-ritonavir plus two NRTIs (lopinavir-ritonavir group), and lopinavir-ritonavir plus efavirenz (NRTI-sparing group). At a median follow-up of 112 weeks, the time to virologic failure was longer in the efavirenz group than in the lopinavir-ritonavir group ($P=0.006$) but was not significantly different in the NRTI-sparing group from the time in either of the other two groups. At week 96, the proportion of patients with < 50 copies/mL of plasma HIV-1 RNA was 89% in the efavirenz group, 77% in the lopinavir-ritonavir group, and 83% in the NRTI-sparing group ($P=0.003$ for the comparison between the efavirenz group and the lopinavir-ritonavir group). The groups did not differ significantly in the time to discontinuation because of toxic effects. At virologic failure, antiretroviral resistance mutations were more frequent in the NRTI-sparing group than in the other two groups. (Riddler SA, Haubrich R, DiRienzo AG, et al. Class-sparing regimens for initial treatment of HIV-1 infection. <i>N Engl J Med</i> 2008 May 15;358(20):2095–106.)</p> <p>The ACTG A5095 study, a randomized, double-blind, placebo-controlled study of treatment-naïve, HIV-1-infected patients compared 3-drug regimen (zidovudine/lamivudine) plus efavirenz with 4-drug regimen ((zidovudine/lamivudine/abacavir plus efavirenz). After a median 3-year follow-up, 26% 25% of patients receiving the 3-drug and 4-drug regimens, respectively, reached protocol-defined virologic failure. In planned subgroup analyses, increased risk for virologic failure was seen in non-Hispanic black patients (adjusted hazard ratio, 1.66; 95% confidence interval, 1.18–2.34; $P = .003$). At 3 years, the HIV-1 RNA level was <200 copies/mL in 90% and 92% of patients receiving the 3-drug and 4-drug regimens, respectively ($P = .59$), and < 50 copies/mL in 85% and 88% of patients ($P = .39$). CD4 cell count increases and grade 3 or 4 adverse events were not significantly different.</p> <p>(Gulick RM, Ribaud HJ, Shikuma CM, et al. Three- vs four-drug antiretroviral regimens for the initial treatment of HIV-1 infection: a randomized controlled trial. <i>JAMA</i> 2006 Aug 16;296(7):769–81.)</p>

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