Profile of etravirine for the treatment of HIV infection

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Abstract: Etravirine is a second-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) with the advantages of in vitro potency against many strains of virus resistant to efavirenz and nevirapine, as well as a higher genetic barrier to resistance. Etravirine is indicated for use in treatment-experienced patients, and the approved dose in adults is 200 mg twice daily. Etravirine should be administered after a meal as bioavailability is significantly reduced when taken in the fasting state. Etravirine is a substrate of CYP3A4, CYP2C9, CYP2C19, and uridine diphosphate glucuronyltransferase, and induces CYP3A4, weakly inhibits CYP2C9 and moderately inhibits CYP2C19. Etravirine may be coadministered with nucleoside/tide reverse transcriptase inhibitors, raltegravir and boosted darunavir, lopinavir, and saquinavir without dosage adjustment. Etravirine should not be given with other NNRTIs, unboosted protease inhibitors, and atazanavir/ritonavir, tipranavir/ritonavir, and fosamprenavir/ritonavir due to unfavorable drug interactions. In randomized, controlled trials, twice daily etravirine combined with darunavir/ritonavir plus optimized background therapy demonstrated better efficacy compared to darunavir/ritonavir plus optimized background therapy alone in treatment-experienced populations out to 96 weeks follow-up. The main etravirine-associated toxicity is mild to moderate self-limiting rash, although severe and sometimes fatal hypersensitivity reactions have been reported. Etravirine offers a potent sequencing option after the development of resistance to first-line NNRTIs, and is a welcome addition to this established drug class.

Keywords: etravirine, review, efficacy, resistance, pharmacology

Introduction

Between 1996 and 1998, 3 non-nucleoside reverse transcriptase inhibitors (NNRTIs), nevirapine (NVP), delavirdine (DLV) and efavirenz (EFV) were approved for the treatment of HIV-1 infection. Delavirdine quickly fell out of favor due to multiple issues, including concerns of viral potency, toxicity, high pill burden of 12 pills daily and inconvenient 3 times daily dosing schedule, and is not recommended as part of an initial regimen.1

Efavirenz and nevirapine share characteristics of viral potency and long plasma half-lives. Efavirenz is available in a fixed-dose combination with tenofovir and emtricitabine, which allows for once daily administration of combination antiretroviral therapy in a single tablet. In the developing world, NVP is commonly co-formulated with stavudine and lamivudine in generic formulations; nevirapine is also an important component of abbreviated protocols to prevent mother-to-child transmission of HIV infection. Advantages to initiating treatment with an NNRTI-based regimen rather than a protease-inhibitor based regimen include lower pill burden and more convenient dosing, improved gastrointestinal tolerability, fewer metabolic side effects, avoidance...
of potentially dangerous inhibitory drug interactions, and lower cost. Since 1998, EFV has been the preferred NNRTI of choice, with NVP classified an alternative agent in this class.1–3

Disadvantages of first generation NNRTIs include low genetic barrier to resistance4 and prevalence of NNRTI-resistant HIV in treatment-naïve patients. A single point mutation in the reverse transcriptase gene at the K103N position confers marked reduction in drug susceptibility with several hundred-fold increases in IC50 or IC90 and pan-class resistance.5,6 Of further concern is that NNRTI-resistant strains may be transmitted. It is estimated that approximately 7% of new HIV-infections in the United States involve NNRTI-resistant strains.7

Efavirenz is associated with central nervous system effects, and is a Category D teratogen. Exposure during the first trimester has been associated with neural tube defects in newborns, and thus EFV should be avoided in pregnant women and in women with high pregnancy potential.6 Nevirapine is associated with hepatotoxicity and should be avoided in patients with high CD4 counts, as well as in those with pre-existing mild to moderate hepatic dysfunction.5

Etravirine is the first next-generation NNRTI to come to market which aims to overcome some of the negative aspects associated with EFV and NVP. Etravirine has demonstrated activity against some strains of virus resistant to other NNRTIs,8 and is approved for use in treatment-experienced adult patients. It is not approved for initial therapy in previously antiretroviral-naïve individuals, and should not be given with NRTIs only when used after an earlier NNRTI-based regimen has failed.9 In this paper, the most recent efficacy and safety data on etravirine in both treatment-naïve and experienced patients will be discussed. In addition, data on the use of etravirine in special populations will be considered, and pharmacology and pharmacokinetics with associated clinical implications will be reviewed.

**Pharmacology**

Etravirine, formerly known as TMC-125 and marketed under the trade name Intelence9, is a di-arylpyrimidine analogue that binds directly to reverse transcriptase and inhibits replication of HIV-1 by causing a disruption of the enzyme’s catalytic site. The inherent molecular flexibility of etravirine relative to other NNRTIs allows the compound to retain its binding affinity to the reverse transcriptase in spite of the binding site changes induced by the presence of common NNRTI resistance mutations.10

**Anti-HIV activity**

In vitro against wild-type HIV-1 strains, etravirine inhibits 50% of viral replication at a median concentration (EC50) of 0.9 to 5.5 nmol/L (ie, 0.4 to 2.4 ng/mL) in acutely infected T-cell lines. Etravirine demonstrates in vitro activity against a range of HIV-1 groups and subgroups, including group M, subtypes A, B, C, D, E, F, and G with EC50 of 0.29 to 1.65 nmol/L. Etravirine demonstrates moderate activity against group O virus with EC50 values of 11.5 to 21.7 nmol/L.9 Etravirine does not have activity against HIV-2.8

Etravirine has in vitro activity against a range of NNRTI-resistant HIV-1 strains. In a panel of viruses with single or double mutations associated with NNRTI resistance, 18 of 25 strains were susceptible to etravirine with EC50 values of <5 nmol/L and fold-change of less than 4 versus wild-type. Three viral strains, Y181I, F227C and L101I/K103N demonstrated significant in vitro resistance to etravirine with EC50 values greater than 10 nmol/L and fold change >10.8

Etravirine is synergistic with zidovudine, and has additive anti-HIV effects with other antiretrovirals, including nucleoside reverse transcriptase inhibitors, NNRTIs and protease inhibitors.8

**Pharmacokinetics**

Etravirine is available as 100 mg tablets. The recommended dose in adults is 200 mg twice daily following a meal. The safety and efficacy of etravirine have not been established in pediatric patients, and hence is not recommended for use in patients under 18 years of age.9

Etravirine is highly protein bound (99.9% in vitro) to albumin and alpha-1-acid glycoprotein, and has an apparent volume of distribution of 422 L. Absorption of etravirine is dependent on food. When administered in a fasted state, the etravirine AUC is reduced by 51% compared to when administered with a standard breakfast. When given with either a light breakfast, an enhanced fiber breakfast or a high fat breakfast containing 70 g fat, the etravirine AUC was decreased 20%, decreased 25% and increased 9%, respectively compared to a standard breakfast. These latter differences are not considered clinically relevant.11 Therefore, etravirine should be administered following a meal for optimal absorption.

In healthy subjects, single-dose etravirine 100 mg was administered in the presence of steady-state ranitidine 150 mg twice daily or omeprazole 40 mg daily. In the presence of ranitidine, etravirine AUC and Cmax were 86% and 94% compared to etravirine alone, and in the presence of omeprazole, etravirine AUC and Cmax were 141% and
117% compared to etravirine alone. Therefore, etravirine may be coadministered with H₂-antagonists and proton-pump inhibitors without dose adjustments.¹²

Etravirine exhibits dose-proportional kinetics in healthy volunteer studies. Time to maximum concentration is 2.5 to 4 hours post-dose, and the mean terminal half-life is 41 hours.⁹ The same daily dose of etravirine results in similar daily exposure whether given in a once or twice daily regimen.¹³ Population pharmacokinetic data from the two DUET trials yielded mean etravirine AUC₁₂₈ of 5506 ng·h/mL and Cₘₐₓ of 393 ng/mL. Interpatient variability of 60% and intrapatient variability of 40% were observed. There was no significant difference in etravirine exposures based on race (blacks, Caucasians, Asians) and gender.¹⁴ There was a trend for higher etravirine levels with increased age, and higher etravirine concentrations were noted with decreasing weight. Patients coinfected with HIV and hepatitis C had higher etravirine exposures, with a mean 1.35-fold increase in AUC compared to non-coinfected subjects.¹⁴

The pharmacokinetics of etravirine 200 mg bid were assessed in 16 HIV negative subjects with mild to moderate hepatic impairment, and compared to 16 healthy matched controls.¹¹ No significant effect on etravirine kinetics was observed in patients with mild hepatic impairment (Child–Pugh A). Patients with moderate hepatic impairment (Child–Pugh B) had similar Cₘᵢₙ and AUC₁₂₈ levels but significantly lower Cₘₐₓ levels compared to healthy controls (Day 1: 0.63; 95% CI 0.47 to 0.85. Day 8: 0.72; 95% CI 0.54 to 0.96). Therefore, etravirine dose adjustment is not required in mild to moderate hepatic impairment.¹⁵

In a case report of a woman with severe hepatic dysfunction (decompensated liver cirrhosis) who received standard doses of tenofovir, etravirine, and darunavir/ritonavir, etravirine levels were measured after 8 months of therapy with a virus load < 50 copies/mL. The etravirine level was 3257 ng/mL, approximately 60 times higher than expected concentrations with standard etravirine dosing. Etravirine was discontinued, and levels measured 2 and 5 weeks later were 931 ng/mL and 100 ng/mL, respectively. Estimated half-life was calculated to be 237 hours. The patient did not experience any clinical adverse events.¹⁶ Because etravirine had not been well studied in this population, caution is advised when using etravirine in persons with severe hepatic dysfunction.

Antiretroviral pharmacokinetics were studied in a 49-year old HIV-positive man virologically suppressed on darunavir/ritonavir 600/100 mg twice daily, etravirine 200 mg twice daily and raltegravir 400 mg twice daily while undergoing hemodialysis three times weekly. The morning dose of the antiretrovirals was taken after completion of the 4-hour morning hemodialysis session. After dialysis, darunavir, etravirine, raltegravir and ritonavir concentrations were decreased by 57%, 29%, 82% and 60%, respectively compared to predialysis levels. A supplemental dose of 600 mg darunavir administered prior to the hemodialysis session was successful in restoring darunavir concentrations approximately equal to expected levels, while administration of a supplemental dose of raltegravir 400 mg was not, likely due to wide intra- and inter-patient variability. Dose supplementation of etravirine was not deemed necessary given the relatively low amount removed during hemodialysis. After 1 year of therapy, the patient maintained viral suppression.¹⁷

Etravirine is classified as a Pregnancy Category B agent.⁸ Data from well-controlled clinical and pharmacokinetic studies in pregnant women are lacking. In rat and rabbit embryofetal studies involving etravirine doses equivalent to 400 mg daily in humans, no adverse fetal effects were observed.¹⁸ Etravirine has been used successfully in combination with boosted darunavir, enfuvirtide and tenofovir/emtricitabine in a pregnant woman with high-level, multiclass resistance. Antiretroviral therapy was started at 25 weeks gestation, full viral suppression was achieved four weeks later with therapeutic maternal plasma levels of darunavir, etravirine, and enfuvirtide. Healthy twin babies were born at 34 weeks gestation, and significant cord blood levels of darunavir, etravirine and ritonavir were measured while enfuvirtide concentrations were undetectable. At 4 months of age, both babies had negative HIV-1 DNA polymerase tests.¹⁹

Efficacy

The antiretroviral efficacy of etravirine has been assessed in various Phase IIa and IIb studies in both treatment naïve and treatment experienced HIV-infected subjects. In an early exploratory phase II study, etravirine demonstrated suboptimal virologic suppression compared to a protease-inhibitor (PI) regimen in PI-naïve subjects with NNRTI resistance. The poorer efficacy in the etravirine arm was thought to be due to a combination of high degree of baseline NRTI resistance and low bioavailability of the older etravirine formulation used.²⁰ A newer formulation of etravirine has since been approved, and was used in larger phase III studies.

A small study of darunavir/ritonavir and etravirine in treatment-experienced patients showed no detrimental pharmacokinetic interaction and a high rate of virologic success, with 9 of 10 subjects at 24 weeks achieving HIV RNA suppression to <40 copies/mL and median CD4 increase of 113 cells/mm³.²¹ These results consequently
sparked interest and recruitment for DUET-1\textsuperscript{22} and DUET-2,\textsuperscript{23} 2 ongoing, large-scale, identically designed, randomized, double-blind, placebo-controlled phase III studies. DUET-1 included 612 subjects from South America, Mexico, France, Thailand and USA, while DUET-2 included 591 subjects from Australia, Canada, Europe, UK and USA.

Patients were eligible if they had been on stable antiretroviral therapy for at least 8 weeks with a viral load >5000 copies/mL at screening, and at least one NNRTI resistance mutation and three or more primary PI resistance mutations. Subjects were randomized to either etravirine 200 mg twice daily or placebo, plus darunavir 600 mg/ritonavir 100 mg twice daily and optimized NRTIs with or without enfuvirtide. At baseline, patients in both studies had been infected with HIV for a median of 14 years, with a median CD4 count of 105 cells/mm\textsuperscript{3} and 4.8 log\textsubscript{10} RNA, and 59% had a Center for Disease Control and Prevention (CDC) C classification. 36% of efavirenz patients and 38% of placebo subjects had an entry viral load \(\geq 100,000\) copies/mL, and 36% and 35% in the etravirine and placebo arms respectively had a CD4 count <50 cells/mm\textsuperscript{3}. Patients had been treated with an average of 12 antiretrovirals and demonstrated extensive HIV resistance, with 36% to 43% having at least 3 NNRTI-associated mutations, over 90% with 4 or more NRTI mutations, and 41% to 44% with 3 or more mutations associated with darunavir resistance. De novo enfuvirtide was used in approximately one quarter of patients.

The primary endpoint in the DUET studies was the proportion of patients achieving viral suppression <50 copies/mL, based on time to loss of virologic response using intention-to-treat analyses (ITT-TLOVR). At 24 weeks, pooled analyses showed that significantly more patients in the etravirine arm compared to placebo achieved viral RNA < 50 copies/mL (59% versus 41%, respectively, \(P < 0.001\));\textsuperscript{24} these findings were similar to the results observed in the individual DUET studies.\textsuperscript{22,23} Pooled results at 48 and 96 weeks confirmed the published 24-week results, with 61% etravirine patients and 40% placebo patients maintaining viral suppression to <50 copies/mL, \(P < 0.0001\) at 48 weeks,\textsuperscript{25} and 57% etravirine patients and 36% placebo patients remaining undetectable at 96 weeks (\(P < 0.0001\)).\textsuperscript{26} Virologic suppression was stable in the pooled cohort from week 48 to week 96; 83% of subjects who achieved viral load <50 copies/mL at 24 weeks, and 91% of subjects with viral load <50 copies/mL at 48 weeks remained undetectable at 96 weeks.\textsuperscript{26}

Baseline viral load, CD4 count, enfuvirtide use and the number of active antiretrovirals in the background regimen were significant predictors for virologic response at 48 weeks for both treatment and placebo groups in pooled analysis.\textsuperscript{27} Even in subjects with no active drugs in the background regimen, a significantly higher virologic response rate was seen at 96 weeks in those treated with etravirine versus placebo (46% versus 6%, \(P < 0.0001\)).\textsuperscript{26} Based on generalized additive modeling analysis, etravirine AUC or \(C_{\text{trough}}\) was not significantly associated with achieving viral load <50 copies/mL at week 48.\textsuperscript{28}

In terms of immunological response, a greater increase in CD4 count from baseline was observed in etravirine subjects compared to placebo, with a mean increases of 86 versus 67 cells/mm\textsuperscript{3} respectively based on pooled analysis at 24 weeks.\textsuperscript{24} This effect was maintained at 48 weeks, with pooled results of mean 98 and 73 cells/mm\textsuperscript{3} increases in treatment versus placebo arms, respectively (\(P < 0.0006\)).\textsuperscript{25}

At 48 weeks, patients treated with etravirine experienced a significantly lower rate of AIDS-defining events (ADE) or death compared to patients on placebo (5.8% versus 9.8% respectively, \(P = 0.0408\)). Time to first confirmed ADE/death was significantly shorter in the placebo group versus etravirine group (\(P = 0.0108\)). Etravirine patients also experienced fewer cumulative hospital days compared to placebo patients over 48 weeks (1702 versus 2747, \(P = 0.0195\)).\textsuperscript{29} By 96 weeks, the differences between the etravirine versus placebo arms had narrowed, but remained slightly more favorable in the etravirine group. The overall proportion of patients with any clinical endpoint by 96 weeks was 8.2% in the etravirine arm and 10.9% in the placebo arm (\(P = 0.27\)). With respect to confirmed or probable AIDS-defining illness, rates of 5.8% and 9.4% were observed in the etravirine and placebo recipients, respectively (\(P = 0.06\)). The time to first confirmed or probable AIDS-defining illness or death remained significantly longer in the etravirine versus placebo group (\(P = 0.05\)). Subjects in the etravirine arm had fewer cumulative days in hospital compared to the placebo group (2737 versus 3453 days), although this difference was no longer statistically significant, with a \(P\)-value of 0.25.\textsuperscript{30}

Results from a phase II noncomparative study of etravirine with raltegravir and darunavir/ritonavir (TRIO trial) in 103 treatment-experienced subjects with multi-drug resistant virus suggested promising efficacy. At baseline, median viral load was 4.2 log\textsubscript{10} copies/mL, CD4 was 255 cells/mm\textsuperscript{3}, and median number of mutations was 4 for protease inhibitors (2 for darunavir), 1 for NNRTIs and 6 for NRTIs. At 24 weeks follow-up, 90% of patients achieved the primary endpoint of HIV viral suppression to less than 50 copies/mL, and a median increase of 99 CD4 cells/mm\textsuperscript{3} from baseline was observed.\textsuperscript{31} Between weeks 24 and 48, 4 patients...
experienced virologic failure, resulting in 86% virologic suppression rate at 48 weeks with a median CD4 increase of 108 cells/mm\textsuperscript{3}.\textsuperscript{32}

Similarly, in a retrospective study involving 53 treatment-experienced patients with multi-class resistance who were co-enrolled in etravirine and raltegravir expanded access programs, 94% achieved undetectable HIV viral load at 24 weeks, with a median CD4 increase of 86 cells/mm\textsuperscript{3}. 81% of this cohort also received de novo darunavir/ritonavir as part of their new background regimen.\textsuperscript{33} Almost identical results were observed in a Spanish cohort of 32 consecutive heavily treatment experienced HIV-positive patients who were treated with etravirine, raltegravir and darunavir 600 mg/100 mg twice daily. At baseline, the median age was 44 years, CD4 261 cells/mm\textsuperscript{3} and HIV RNA 4.2 log\textsubscript{10} copies/mL. Median time on antiretroviral therapy was 13 years, with an average of nine prior HAART regimens; 50% were enfuvirtide-experienced, and 44% had been on prior tipranavir therapy. All patients had triple-class resistance; 3 had etravirine resistance mutations. All subjects were darunavir-naïve, and had a median of one darunavir-resistance mutation. At week 24, 94% of subjects achieved undetectable viral load, with a median CD4 increase of 103 cells/mm\textsuperscript{3}.\textsuperscript{34}

The global etravirine early access program (TMC125-C214) involved triple-class antiretroviral experienced patients who had received at least two prior PI-containing regimens. At screening, patients with undetectable viral loads were permitted to switch from enfuvirtide to etravirine for reasons of intolerance or simplification; optimization of other components of the background regimen was also allowed at this time. Follow-up was reported for 37 patients, 36 (97%) of whom used etravirine in combination with darunavir/ritonavir; 62% also used raltegravir, 16% used maraviroc, and 89% used concomitant NRTIs. At 24 weeks, 35 (95%) of subjects maintained viral suppression <50 copies/mL; one subject had a viral load of 50 copies/mL, and the other had missing data at week 24, but viral load <50 copies/mL at week 12.\textsuperscript{35}

The GRACE study was a multi-center, 48-week, open-label phase IIIb study assessing the efficacy and safety of darunavir/ritonavir plus optimized background regimen in treatment-experienced patients. This study was specifically designed to enroll a high proportion of treatment-experienced women and people of color. A pre-planned subgroup analysis evaluated virologic response and safety in subjects who received etravirine as a component of their optimized background. Of 429 subjects who enrolled in GRACE, 207 received at least one dose of etravirine. Of these, 119 (57%) were female, of whom 70.6% were black and 16% were Hispanic. Overall baseline viral load was 4.6 log\textsubscript{10} copies/mL, CD4 187 cells/mm\textsuperscript{3}, and median fold-change in etravirine susceptibility was 1.4. At 48 weeks, the overall response was 49.5% in the intention to treat, time-to-loss of virologic response (ITT-TLOVR) and 76.4% intention-to-treat censored group who discontinued for reasons other than virologic failure. Similar virologic response rates were observed for women and men in this subgroup. In a post hoc multivariate analysis of all GRACE participants, inclusion of etravirine was one of the factors significantly predictive of virologic response, with an odds ratio of 1.56, \( P = 0.0424.\textsuperscript{36}

Pediatric experience with etravirine is extremely limited. One case reported the use of darunavir/ritonavir and etravirine in a premature male infant vertically infected with multi-drug resistant HIV-1. The child was delivered at 33 weeks by emergency cesarean section to a treatment-experienced mother with a viral load of 4.4 log\textsubscript{10} copies/mL and CD4 76 cells/mm\textsuperscript{3} at delivery; genotypic testing revealed the presence of 11 mutations at the reverse transcriptase site (D67N, T69N, K70R, A98S, K103N, V118I, V179E, M184V, Y188L, T215F, K219E) as well as the protease site (L10I, K20M, M36I, M46I, L63P, A71V, G73S, V77I, I84V, L90M, I93L). At birth, the patient’s viral load was 5.92 log\textsubscript{10} copies/mL, and genotypic testing showed identical resistance mutations as the mother. During the first year and a half of life, the patient was sequentially treated with numerous RTIs, lopinavir/ritonavir and enufvirtide, but his clinical condition deteriorated rapidly. At 21 months of age, his CD4 was 10 cells/mm\textsuperscript{3}, viral load was 5.80 log\textsubscript{10} copies/mL, and genotypic testing showed the same resistance mutations at birth plus gp41-associated mutations. At 24 months of age, the patient began darunavir 150 mg/ritonavir 20 mg twice daily plus etravirine 50 mg twice daily (increased to 100 mg twice daily after 2 months) through compassionate access plus lamivudine 4 mg/kg twice daily. Pharmacokinetic assessment at day 70 showed darunavir and etravirine trough plasma concentrations of 5270 and 650 ng/mL, respectively, which are within reported therapeutic ranges. Over the following 15 months, the antiretroviral regimen was well tolerated, the patient’s condition significantly improved with normalization of numerous laboratory parameters, and an undetectable viral load was achieved and maintained from 12 months onwards.\textsuperscript{37}

In France, 12 heavily pretreated, perinatally infected adolescents received the combination of darunavir/ritonavir, etravirine and raltegravir through a compassionate program between October 2006 and December 2007.
At baseline, the median age was 15 years (range 12 to 17), weight 48 kg (range 28.5 to 72), CD4 124 cells/mm$^3$ (range 13 to 484) and viral load 5.27 log$_{10}$ copies/mL (range 4.33 to 6.1). All patients had received antiretroviral therapy for a median of 15 years (range 10 to 17), including a median of 6 NRTIs, 1 or 2 NNRTIs and 4 PIs, and 6 had previously received enfuvirtide. Standard adult doses of antiretrovirals were used in the majority of patients. After a median follow-up of 12 months, viral load was <400 copies/mL in 11 patients, with 6 having <50 copies/mL. Median CD4 count increased to 500 cells/mm$^3$ by month 9. The combination was very well tolerated, with one patient discontinuing darunavir/ritonavir because of diarrhea and vomiting. No grade 3 to 4 laboratory parameters were noted.

Clinical safety
In the DUET studies, pooled analysis at 96 weeks indicated that the incidence and severity of adverse events (AEs), serious AEs, laboratory abnormalities and study discontinuations related to AEs were comparable between the etravirine and placebo groups except for rash. The most common AEs observed in the etravirine and placebo groups were rash (21 versus 12, $P = 0.0001$), diarrhea (19% versus 24%) and nausea (15% versus 14%). The incidence and severity of nervous system and psychiatric events, most commonly headache and insomnia, liver enzyme and lipid elevations were similar between the etravirine and placebo groups.

Most rashes observed with etravirine were maculopapular, of mild-moderate severity (1.3% grade 3, no grade 4 events), occurred at a median of 14 days after therapy initiation, and lasted a median 15 days. Most rashes resolved with continued treatment, and only 2.2% of patients discontinued etravirine due to rash. No cases of Stevens-Johnson syndrome, erythema multiforme or toxic epidermal necrolysis were reported in the etravirine group. There was a higher incidence of rash in women than men (30% versus 18%, $P = 0.0365$), but rash severity was similar. There was no relationship between rash and etravirine pharmacokinetic exposure, and neither CD4 cell count nor history of NNRTI-related rash were predictive of rash with etravirine.

In August 2009, the manufacturer issued a drug warning regarding the safety of etravirine in light of post-marketing reports of severe skin and hypersensitivity reactions. Cases included severe, potentially life-threatening and fatal reports of Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme. In addition, hypersensitivity reactions characterized by rash, constitutional findings, and occasional organ dysfunction including hepatic failure were also reported. Prescribers are now advised to discontinue etravirine immediately if signs or symptoms of severe skin or hypersensitivity reactions develop.

Resistance
Multiple mutations have been reported to have varying degrees of impact on the activity of etravirine. The package insert includes a standard list of NNRTI-associated mutations, is somewhat confusing because the NVP- and EFV-selected mutation K103N is included in the list. Importantly, K103N, which is the most common mutations selected by previous exposure to either EFV or NVP, does not limit the activity of etravirine.

In addition, the common EFV- and NVP-selected mutations G190A/S have been found not to have any limiting effect on the activity of etravirine. In general, the more other NNRTI-selected mutations present, the less likely is it for an etravirine-containing regimen to result in HIV RNA levels <50 copies/mL. However, not all mutations exert the same limiting effect on the activity of etravirine. The mutations L100I, K101P, Y181C/I/V, and M230L are the most limiting to the activity of etravirine. Indeed, even one of these mutations is sufficient to reduce the likelihood of getting HIV RNA levels to <50 copies/mL to only about 50%. The most common of these mutations is the mutation Y181C. At least one of the these six very limiting mutations occurs about 32% of the time in persons failing on a nevirapine-containing regimen compared to 10% of the time in persons failing on an efavirenz-containing regimen.

Whether this difference will be shown to be clinically relevant as a sequencing strategy of starting with efavirenz as opposed to starting with nevirapine, remains to be seen.

Drug interactions
Etravirine is a substrate of CYP3A4, CYP2C9, CYP2C19 and uridine diphosphate glucuronosyltransferase (UDPGT). Etravirine is an inducer of CYP3A4, a weak inhibitor of CYP2C9 and a moderate inhibitor of CYP2C19. Etravirine has no clinically relevant effect on CYP1A2 or CYP2D6. Etravirine may be coadministered with tenofovir, NRTIs, and the boosted protease inhibitors darunavir, lopinavir, and saquinavir, enfuvirtide and raltegravir without dosage adjustment. Etravirine should not be given with NNRTIs, unboosted PIs, as well as atazanavir/ritonavir, tipranavir/ritonavir and fosamprenavir/ritonavir due to unfavorable drug interactions.

In a crossover study of healthy volunteers, no clinically relevant interaction was observed between etravirine 800 mg (Phase II formulation) twice daily with food and...
enteric-coated didanosine 400 mg once daily given 2 hours before etravirine on an empty stomach.\textsuperscript{45} Coadministration of tenofovir 300 mg daily plus etravirine 200 mg twice daily led to 19\% reduction in C\textsubscript{max} and AUC and 18\% reduction in C\textsubscript{min} of etravirine, while tenofovir pharmacokinetic parameters increased 15\%.\textsuperscript{46} Population pharmacokinetic data from a subset analysis of the DUET trials suggest that coadministration of tenofovir was associated with a 26\% reduction in etravirine AUC.\textsuperscript{14} In the same subset analysis, use of enfuvirtide had no effect on etravirine AUC.\textsuperscript{14} All of these effects are not considered clinically significant.

In a pharmacokinetic study involving HIV-infected subjects, the addition of etravirine 200 mg twice daily to darunavir 600 mg/ritonavir 100 mg twice daily led to approximately 30\% reduction in etravirine exposures compared to historical controls, while darunavir pharmacokinetics were unchanged.\textsuperscript{47} In healthy volunteers, coadministration of etravirine 200 mg twice daily and lopinavir/ritonavir tablets 400/100 mg twice daily for 8 days resulted in reductions of 45\%, 30\% and 35\% in etravirine C\textsubscript{min}, C\textsubscript{max} and AUC, respectively, and decreases of 20\%, 11\% and 13\% in lopinavir C\textsubscript{min}, C\textsubscript{max} and AUC, respectively, compared to each drug administered alone.\textsuperscript{48} Etravirine AUC was reduced 33\% in the presence of saquinavir 1000/ritonavir 100 mg twice daily.\textsuperscript{9} None of these effects are considered clinically meaningful.\textsuperscript{3,48}

Healthy subjects who received raltegravir 400 mg twice daily and etravirine 200 mg twice daily for 4 days had modest decreases in raltegravir concentrations, with reductions of 10\%, 11\% and 34\% in AUC, C\textsubscript{max} and C\textsubscript{12 hours}, respectively compared to raltegravir alone, while etravirine levels were not altered.\textsuperscript{49} In a cohort of 29 HIV-positive subjects receiving regimens including raltegravir, raltegravir/darunavir 600 mg/ritonavir 100 mg twice daily, or raltegravir/darunavir/ritonavir/etravirine twice daily, no differences in raltegravir C\textsubscript{tough} were noted between the groups.\textsuperscript{50}

Atazanavir trough levels are reduced approximately 40\% to 50\% when administered both alone and ritonavir-boosted in the presence of etravirine. Indinavir concentrations are reduced 46\% and saquinavir concentrations are reduced 52\% with steady-state etravirine, while etravirine exposures are increased 51\% when co-administered with indinavir.\textsuperscript{51} Coadministration of tipranavir/ritonavir results in a 76\% reduction in AUC and a 82\% reduction in C\textsubscript{min} of etravirine. In an open-label interaction trial of HIV-infected subjects on stable fosamprenavir 700 mg plus ritonavir 100 mg twice daily, addition of etravirine 800 mg (Phase II formulation) bid for 14 days led to increases of 69\%, 62\% and 77\% in AUC, C\textsubscript{max} and C\textsubscript{min} of amprenavir, respectively, compared to boosted fosamprenavir alone. Etravirine parameters were similar to historical controls.\textsuperscript{52} Etravirine should not be used in combination with atazanavir, indinavir, saquinavir, tipranavir, fosamprenavir due to these interactions.

Administration of single-dose etravirine 900 mg in the presence of steady-state EFV 600 mg daily or NVP 200 mg twice daily resulted in significant reductions in etravirine exposure. Etravirine AUC was reduced 41\% and 55\% and C\textsubscript{max} was reduced 18\% and 36\% with EFV and NVP, respectively.\textsuperscript{53} Consequently, etravirine should not be used in combination with either EFV or NVP.

In a healthy volunteer study, etravirine was administered 400 mg daily or 200 mg twice daily for 14 days at baseline and then again after 14 days of EFV treatment to assess for any continued effects of EFV enzyme induction on etravirine metabolism. Steady-state etravirine parameters were significantly reduced after EFV intake in both the once- and twice-daily dosing arms; etravirine AUC was reduced 28\% to 29\%, C\textsubscript{max} was reduced 28\% to 29\%, and C\textsubscript{tough} was reduced by 33\% to 37\%. These changes are likely not clinically significant as all subjects had etravirine levels well above the protein binding-adjusted EC\textsubscript{50} of 4 ng/mL and concentrations were comparable to those observed in clinical trials where etravirine was co-administered with darunavir/ritonavir. Therefore, the authors suggest that switching from EFV to etravirine once or twice daily may be done without dose adjustment.\textsuperscript{53}

In a healthy volunteer study, steady state etravirine concentrations were increased by 75\%–109\% in the presence of fluconazole 200 mg daily for 9 days. This combination was well tolerated; a post-hoc analysis of adverse events in DUET-1 and DUET-2 over 96 weeks in patients with or without concomitant fluconazole showed no difference in safety parameters.\textsuperscript{54} In healthy volunteers, coadministration of etravirine 200 mg twice daily plus voriconazole 200 mg twice daily for 9 days resulted in increases of 52\%, 26\% and 36\% of etravirine C\textsubscript{min}, C\textsubscript{max} and AUC, respectively, while voriconazole C\textsubscript{min} and AUC increased 23\% and 14\% respectively (only in subjects who were not carriers of the CYP2C19*2 allele) compared to either drug administered alone. In this study, the combination was well tolerated.\textsuperscript{54} However, in clinical practice, a reduction in dosage of both agents may be required, and therapeutic drug monitoring of both agents should be considered if available. Etravirine may be coadministered with methadone and oral contraceptives without dosage modification.\textsuperscript{55} A summary of drugs that should not be co-administered with etravirine is provided in Table 1.
The advent of a second-generation NNRTI represents a welcome advance in drug development in a well-established class. Etravirine is indicated for use in treatment-experienced patients, and offers a potent sequencing option after the development of resistance to first-line NNRTIs. Experience is limited in specific subpopulations, but preliminary data in pregnancy, pediatric and adolescent patients, end-stage liver disease and hemodialysis are promising. Etravirine is generally well tolerated, and has a manageable drug interaction profile.

Etravirine may also be considered as a suitable replacement for patients who are virally suppressed on efavirenz or nevirapine but have developed toxicities, or women on efavirenz who wish to become pregnant. When switching a patient from efavirenz to etravirine, etravirine may be instituted at its regular dose without concern of enduring effects of efavirenz-mediated enzyme induction. While the manufacturer is not pursuing a once daily dosing indication for etravirine, pharmacokinetic data support this option, which offers increased flexibility when designing regimens for patients with adherence challenges. The current pill burden of etravirine is higher compared to first-line NNRTIs efavirenz and nevirapine (4 pills versus 1 or 2 pills daily), although it is comparable to the pill burden associated with other agents often used in treating experienced patients such as boosted darunavir or tipranavir (4 to 6 pills daily). Etravirine tablets may also be dispersed in water for patients who are unable to swallow tablets.

The fact that etravirine retains activity in the presence of the commonly EFV- and NVP-selected mutations K103N and G190A/S increases substantially the utility of this antiretroviral. However, multiple NNRTI-selected mutations, often interacting in complex and difficult to predict ways, will limit the activity of etravirine by varying amounts. Consequently, a reliable resistance test, such as either the PhenoSense® assay or the virco®TYPE HIV-1 assay should be obtained prior to the initiation of therapy with etravirine, especially in situations in which genotypic resistance testing has demonstrated multiple NNRTI-selected mutations.

Summary

Etravirine is a second generation NNRTI with the advantages of in vitro potency against many strains of virus resistant to efavirenz and nevirapine, as well as a higher genetic barrier to resistance. In randomized, controlled trials, twice daily etravirine (combined with darunavir/ritonavir) demonstrated efficacy compared to placebo in treatment-experienced populations out to 96 weeks follow-up. The main toxicity is mild to moderate self-limiting rash, although severe and sometimes fatal hypersensitivity reactions have been reported. Etravirine is a substrate and inducer of CYP3A4, with a similar interaction profile as other NNRTIs. Etravirine is indicated for use in treatment-experienced patients, and offers a potent sequencing option after the development of resistance to first-line NNRTIs.

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Table 1 Drugs that should not be co-administered with etravirine

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