

Role of etravirine in the management of treatment-experienced patients with human immunodeficiency virus type 1

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Abstract: Etravirine is an oral diarylpyrimidine compound, a second-generation human immunodeficiency virus type 1 (HIV-1) non-nucleoside reverse transcriptase inhibitor (NNRTI) with expanded antiviral activity against NNRTI-resistant HIV-1, to be used in combination therapy for treatment-experienced patients. Compared with first-generation NNRTIs, etravirine has a high genetic barrier to resistance, and is better tolerated without the neuropsychiatric and hepatic side effects of efavirenz and nevirapine, respectively. Its safety profile is comparable to placebo with the exception of rash, which has been mild and self-limited in the great majority of patients. In phase III clinical trials among treatment-experienced patients harboring NNRTI-resistant HIV-1, etravirine in combination with an optimized background regimen (OBR) that included ritonavir-boosted darunavir demonstrated superior antiviral activity than the control OBR. In addition, patients on the etravirine arm had fewer AIDS-defining conditions, hospitalizations, and lower mortality compared with the OBR control arm.

Keywords: HIV, antiretroviral therapy, non-nucleoside reverse transcriptase inhibitor

Introduction

Over the last 14 years, combination antiretroviral therapy has led to adequate suppression of human immunodeficiency virus (HIV) replication, immunologic recovery, and a dramatic decline in morbidity and mortality among HIV-infected individuals in the industrialized world, and to a lesser degree in developing countries.¹⁻⁵ The goal of antiretroviral therapy is to suppress HIV replication to undetectable levels. The International AIDS Society-USA Panel currently recommends the combination of 2 reverse transcriptase inhibitors and either the non-nucleoside reverse transcriptase inhibitor (NNRTI) or the ritonavir-boosted protease inhibitor (PI) as the initial therapy.⁶ However, virologic suppression is not always achieved or maintained due to a variety of reasons, such as poor tolerability due to side effects leading to poor compliance, drug-to-drug interactions, and HIV drug resistance. Over the last few years, the use of an NNRTI, such as efavirenz in industrialized countries and nevirapine in resource-limited settings, had been preferred for first-line treatment due to its high potency and low pill burden.⁶ However, efavirenz and nevirapine have a low genetic barrier to resistance, so that a single amino acid substitution in the viral reverse transcriptase (RT), such as K103N, leads to profound reduction in viral susceptibility to both drugs, conferring class-wide drug resistance.⁷ Transmitted NNRTI drug resistance has been increasing in adolescents and young adults in industrialized countries.⁸⁻¹⁰ Additionally, transmitted NNRTI drug resistance, in particular the mutation in position K103N, has been shown to persist several years in the absence of drug pressure.¹¹ In developing

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countries where single-dose nevirapine is being used to prevent mother-to-child HIV transmission, the prevalence of nevirapine drug resistance has been as high as 35% and 52% among women and infants exposed to single-dose nevirapine, respectively.¹²

Etravirine (Intelence®; Tibotec Therapeutics, Raritan, New Jersey), formerly known as TMC125, is a second-generation NNRTI that was approved by the US Food and Drug Administration (FDA) in January 2008 for use in HIV-1-infected individuals at a dose of 200 mg (two 100-mg tablets) twice a day. Its indication is for treatment-experienced adults with evidence of NNRTI drug resistance.¹³ Etravirine is a diarylpyrimidine compound that emerged after a long parallel screening process, involving testing candidate compounds from a series of diarylpyrimidines against wild-type and selected single- and double-mutant, NNRTI-resistant HIV-1 isolates.¹⁴ Etravirine is highly active against wild-type HIV-1 with a 50% effective concentration (EC_{50}) of 1.4–4.8 nM and shows some activity against HIV-2 with an EC_{50} of 3.5 μ M. In addition, etravirine retained activity with an $EC_{50} < 100$ nM against 97% of 1,081 clinically derived recombinant viruses resistant to at least one of the first-generation NNRTIs.^{14,15} Etravirine has a diarylpyrimidine-based structure with molecular flexibility that allows it to accommodate to mutational changes in the RT binding pocket.¹⁶ The NNRTI binding sites are located in codons 100 to 110 and 180 to 190. The presence of the K103N and Y181C mutations reduces the NNRTI binding affinity, leading to drug resistance.¹⁷ Etravirine has a higher genetic barrier to HIV drug resistance, with activity against efavirenz- and nevirapine-resistant HIV-1 isolates harboring the K103N and Y181C mutations.¹⁴ Etravirine, as other NNRTI, is a noncompetitive inhibitor of the HIV RT enzyme; by binding to the hydrophobic pocket proximal to the active site, it causes a conformational change in the enzyme and disrupts its function.¹⁶ Etravirine has an ability to bind to the RT enzyme even in the presence of such mutations. Its structure allows etravirine to bind to the enzyme in several modes due to the conformational adaptation based on changes in the binding pocket.¹⁶ The torsional flexibility allows etravirine to reorient itself and bind to the enzyme despite the presence of NNRTI resistance mutations.¹⁸

Pharmacology

Pharmacokinetics

Early phase I/II studies were conducted with a polyethylene glycol (PEG) capsule formulation (PEG4000) with low bioavailability and high pill burden, needing 900 mg

twice a day to provide reliable pharmacokinetic profile.¹⁹ The PEG formulation resulted in a high incidence of gastrointestinal side effects.²⁰ A dose-finding, phase II, randomized clinical trial (TMC125-C223) comparing 2 doses of the TF035 formulation (granular layered) of etravirine at 400 or 800 mg twice a day in addition to 2 or more approved antiretroviral agents selected the 800 mg twice a day for further development.²¹ A solid dispersion formulation using spray-drying technology was developed to improve etravirine bioavailability and reduce pill burden. A multiple-dose bioavailability study in HIV-infected individuals demonstrated similar steady-state pharmacokinetic exposure for the solid dispersion formulation at a dose of 200 mg twice a day compared with the 800 mg twice a day of the granular-layered formulation with reduced interpatient variability.²²

Etravirine is currently formulated as a 100-mg tablet that has a more reliable pharmacokinetic profile without the frequent gastrointestinal side effects associated with the PEG capsule formulation. The dose approved by the FDA is 200 mg twice a day. When etravirine is administered under fasting conditions, the systemic exposure is decreased by 50%; therefore, etravirine should be administered after meals.²³ In patients who have trouble swallowing tablets, the 100-mg tablet can be dispersed in water with comparable bioavailability to the swallowed tablet.^{23,24}

Population pharmacokinetic analysis of pooled data from DUET-1 and DUET-2 among 574 patients revealed an etravirine mean (SD) AUC_{12h} and C_{min} of 5,501 (4,544) ng·h/mL and 393 (378) ng/mL, respectively.²⁵ In addition, the pooled analysis revealed a mean (SD) C_{max} of 797 (668) ng/mL at week 24. Clearance (CL/F) was estimated to be 43.7 L/h, and the intersubject variability on CL/F was 60% with a 40% intrasubject variability on fraction absorbed.^{25,26} It is important to mention that patients in both DUET trials were also treated with darunavir 600 mg/ritonavir 100 mg/twice a day, drugs that interact with etravirine.

Etravirine is 99.6% protein bound, primarily to albumin.¹³ Maximal plasma concentration T_{max} is reached in 2.5–4 hours, with an elimination half-life of 30–40 hours, which suggests that once-a-day administration is a feasible option.^{19,26} A multiple-dose pharmacokinetic study comparing etravirine monotherapy 200 mg twice a day with 400 mg once a day in healthy HIV-negative individuals was conducted. The systemic exposure was similar with a mean (SD) AUC_{12} of 8,195 (2,428) ng/h/mL and mean (SD) AUC_{24} of 17,220 (5,009) ng/h/mL for the twice-a-day vs once-a-day dose, respectively.²⁶ The C_{min} of etravirine was approximately 27%

lower for the once-a-day dose, and the C_{\max} of etravirine was approximately 45% higher for the once-a-day dose.²⁶

The pharmacokinetics of etravirine is unchanged in patients with mild to moderate hepatic impairment. Etravirine has reduced CL/F in patients with hepatitis B or C coinfection; however, no dose adjustment is necessary.²⁷ The pharmacokinetics of etravirine has not been studied in patients with renal impairment.¹³

Pharmacodynamics

The DUET-1 and DUET-2 multisite, double-blind, randomized, placebo-controlled phase III trials demonstrated superior virologic response when etravirine was compared with placebo, and when added to a combination regimen that included ritonavir-boosted darunavir.²⁸⁻³⁰ Factors predicting virologic response, defined as the proportion of patients with viral loads less than 50 copies/mL at 48 weeks, included lower baseline viral load, higher baseline CD4 cell count, better adherence, number of active agents in the background regimen, and baseline fold change (FC) in EC_{50} to etravirine.³⁰ Pharmacokinetic parameters of AUC_{12} and C_{\min} did not predict virologic suppression at week 48.³⁰ Other factors, such as age, sex, race, and HIV clade, were not predictive of virologic response to etravirine at 48 weeks.³⁰

Metabolism

Etravirine is a substrate of the hepatic cytochrome P450, and primarily metabolized by CYP3A4, CYP2C9, and CYP2C19, with its metabolites undergoing glucuronidation. Etravirine is an inducer of CYP3A4 and an inhibitor of CYP2C9, CYP2C19, and P-glycoprotein; therefore, coadministration of drugs that are substrates of CYP3A4, CYP2C9, and CYP2C19 or are transported by P-glycoprotein may alter the therapeutic effect or adverse reaction profile of the coadministered drug.^{13,26} Etravirine concentrations may also be affected by drugs that alter CYP3A4, CYP2C9, or CYP2C19 activity and are expected to be higher in patients with reduced CYP2C9 or CYP2C19 activity.

Drug interactions

Since etravirine has mixed effects on the isoenzymes of the cytochrome P450, the potential drug interactions with NNRTIs, PIs, azoles antifungals, clarithromycin, rifamycins and other drugs, are extensive (Table 1). Etravirine should not be coadministered with unboosted PIs or with ritonavir-boosted tipranavir. Coadministration with ritonavir-boosted fosamprenavir results in high exposure to fosamprenavir with potential toxicity; therefore, coadministration is discouraged.

Coadministration with atazanavir 300 mg/ritonavir 100 mg results in a decrease in the atazanavir C_{\min} by 38%; therefore, the authors suggest increasing the atazanavir dose to 400 mg with 100 mg of ritonavir.^{13,26} Coadministration of etravirine and the new integrase inhibitors (raltegravir and elvitegravir) has been evaluated in healthy volunteers. When raltegravir and etravirine were used at the recommended doses of 400 and 200 mg twice a day, respectively, there was a slight increase in etravirine exposure and a small decrease in the raltegravir exposure that were not clinically significant.³¹ Similarly, no clinically relevant interaction was observed when elvitegravir and ritonavir at the dose of 150 and 100 mg once a day, respectively, were coadministered with etravirine 200 mg twice a day.³²

Coadministration of etravirine with CYP450 inducers, such as the anticonvulsants phenobarbital, phenytoin, and carbamazepine, as well as coadministration with the rifamycins, rifampin or rifapentine, is contraindicated. However, rifabutin, a substrate and an inducer of CYP3A4, can be used in conjunction with etravirine without clinically significant interaction.¹³

Fluconazole and voriconazole are inhibitors of CYP3A, CYP2C9, and CYP2C19, and coadministration with etravirine resulted in a slight increase in etravirine steady-state exposure. The voriconazole and fluconazole exposures were virtually unchanged; therefore, dose adjustment is not necessary.^{26,33} Itraconazole and ketoconazole are substrates and potent inhibitors of CYP3A4 and could increase the etravirine exposure. In addition, etravirine could decrease the exposure of ketoconazole and itraconazole; therefore, caution should be exercised when etravirine is coadministered with these antifungals.³⁴ Clarithromycin is an inhibitor of CYP3A4 and when coadministered with etravirine, caused a 40% increase in etravirine exposure. The overall exposure of clarithromycin was reduced by 59%, while the 14-hydroxy-clarithromycin exposure was increased. Since the 14-hydroxy-clarithromycin has decreased activity against *Mycobacterium avium* complex, it is recommended to consider azithromycin as an alternative treatment for *M. avium* complex infection.²⁶ For a comprehensive review of the etravirine interactions with different medications, the reader is referred to the etravirine prescribing information.¹³

Efficacy studies

A double-blind, phase IIa clinical trial among HIV-infected, treatment-naïve subjects randomized 2:1 to receive either etravirine 900 mg twice a day (PEG 4000 formulation) or

Table 1 Significant etravirine drug interactions^{13,26,34,47}

| Drug | Effect on ETR | Effect on drug | Comment |
|--|--|---|--|
| Protease inhibitors ^a | | | |
| Saquinavir/ritonavir 1000/100 mg twice a day | 33% ↓ AUC, 29% ↓ C _{min} | 20% ↓ C _{min} | No dose adjustment |
| Atazanavir/ritonavir 300/100 mg every day | 30% ↑ in C _{max} ^a AUC and C _{min} | 38% ↓ in C _{min} , 14% ↓ in AUC | ↑ ATV dose ^b |
| Fosamprenavir/ritonavir 700/100 mg twice a day | No effect | ↑ 62%–77% C _{max} ^a , AUC and C _{min} | Avoid use |
| Lopinavir/ritonavir ^c 400/100 mg twice a day | 35% ↓ AUC, 45% ↓ C _{min} | 13% ↓ AUC, 20% ↓ C _{min} | No dose adjustment |
| Tipranavir/ritonavir 500/200 mg twice a day | 76% ↓ AUC, 82% ↓ C _{min} | 24% ↑ C _{min} | Avoid use |
| Darunavir/ritonavir 600/100 mg twice a day | 37% ↓ AUC, 49% ↓ C _{min} | 15% ↑ AUC | No dose adjustment |
| Reverse transcriptase inhibitors | | | |
| Didanosine 400 mg every day | No effect | No effect | No dose adjustment |
| Tenofovir DF 300 mg every day | 19% ↓ AUC, 18% ↓ C _{min} | 19% ↑ C _{min} | No dose adjustment |
| Integrase inhibitor | | | |
| Raltegravir 400 mg twice a day | 17% ↑ C _{min} | 34% ↓ C _{min} | No dose adjustment |
| Elvitegravir/ritonavir 150/100 mg every day | No effect | No effect | No dose adjustment |
| CCR5 antagonists | | | |
| Maraviroc 300 mg twice a day | No effect | 53% ↓ AUC, 39% ↓ C _{min} | ↑ Maraviroc to 600 mg twice a day ^d |
| Other drugs | | | |
| Rifabutin 300 mg every day | 35% ↓ C _{min} , 37% ↓ AUC | 24% ↓ C _{min} | No dose adjustment |
| Clarithromycin 500 mg twice a day | 42% ↑ AUC, 46% ↑ C _{min} | 39% ↓ AUC, 53% ↓ C _{min} | Avoid use ^e |
| Omeprazole 40 mg every day | 41% ↑ AUC | Not available | No dose adjustment |
| Ranitidine 150 mg twice a day | 14% ↓ AUC | Not available | No dose adjustment |
| Atorvastatin 40 mg every day | No effect | 37% ↓ AUC | No dose adjustment |
| Paroxetine 20 mg every day | No effect | No effect | No dose adjustment |
| Methadone 60–130 mg/day | No effect | No effect | Monitor for withdrawal |
| Sildenafil 50 mg single dose | No effect | 57% ↓ AUC | Sildenafil dose needs to be ↑ |

^aUnboosted protease inhibitors should not be used with etravirine; ^bTo 400 mg with 100 mg of ritonavir every day; ^cTablet; ^dIn the absence of boosted protease inhibitor. If ritonavir-boosted darunavir is combined with etravirine and maraviroc, the maraviroc dose should be 150 mg twice a day; ^eConsider using azithromycin; ^fMethadone maintenance dose may need to be adjusted.

Abbreviations: AUC, area under the plasma concentration-time curve; C_{min} and C_{max}, minimum and maximum plasma concentrations; ATV, atazanavir; ETR, etravirine; DF, disoproxil fumarate.

matched placebo as monotherapy was conducted as a proof of concept.¹⁹ After 7 days, patients treated with etravirine ($n = 12$) had a mean decrease in plasma HIV RNA of 1.99 log₁₀ copies/mL compared with 0.06 log₁₀ copies/mL in the placebo arm ($n = 7$; $P < 0.001$).¹⁹

In an open-label, phase IIa trial, 16 individuals receiving either efavirenz or nevirapine on virologic failure, defined as having HIV RNA viral load >2000 copies/mL and documented high-level phenotypic NNRTI resistance, substituted their failing NNRTI for etravirine 900 mg twice a day for 7 days. After 7 days of treatment, a median 0.89 log₁₀ copies/mL decline in HIV RNA load was observed and 7 individuals (44%) had greater than 1 log₁₀ decline in HIV RNA load.²⁰

TMC125-C223 was an open-label, partially blinded, phase II randomized clinical trial, which evaluated the efficacy of 2 doses of the TF035 (granular layered) formulation

of etravirine at 400 or 800 mg twice a day in addition to 2 or more approved antiretroviral agents, such as nucleoside reverse transcriptase inhibitors (NRTIs) and lopinavir/ritonavir and/or enfuvirtide. The comparator arm was an optimized regimen consisting of 3 or more FDA-approved drugs from 2 or more classes.²¹ The 199 patients studied were randomized 2:2:1 to etravirine 400 mg, 800 mg, and control, and had evidence of genotypic resistance to first-generation NNRTIs and at least 3 primary PI mutations. The mean reduction in HIV RNA from baseline at week 24 was 1.04, 1.18, and 0.19 log₁₀ copies/mL for etravirine 400 mg twice a day, 800 mg twice a day, and the control group, respectively ($P < 0.05$ for both etravirine groups compared with control).²¹ There was no significant difference in efficacy between the 2 etravirine doses; however, in patients not treated with enfuvirtide, or in patients treated

with only 1 active agent (other than etravirine), the 800-mg dosage had greater virologic success.²¹ TMC125-C227 was a phase II, randomized, controlled, open-label 48-week trial comparing the efficacy of etravirine with an investigator-selected PI in NNTRI-resistant, PI-naive HIV-infected patients. Patients were randomized to etravirine 800 mg twice a day ($n = 59$) or the control PI ($n = 57$), plus 2 NRTIs.³⁵ This trial was prematurely stopped when an unplanned interim analysis revealed suboptimal virologic response in individuals receiving etravirine in comparison with the control PI arm. The suboptimal virologic response in the etravirine arm was attributed to the high level of baseline NRTI and NNRTI resistance that made this arm virologically inferior to the PI-based control regimen. Therefore, the use of etravirine plus NRTIs alone will be suboptimal in PI-naive patients with first-line virologic failure on an NNRTI-based regimen.³⁵

The DUET-1 and DUET-2 are multinational, randomized, double-blind, placebo-controlled phase III trials with identical design and conducted in different areas of the world. Treatment-experienced adults with virologic failure on stable antiretroviral therapy, documented NNRTI genotypic resistance, viral load over 5000 copies/mL, and 3 or more primary PI mutations were randomly assigned to receive 200 mg of etravirine or placebo twice a day. All patients also received 600 mg of darunavir with 100 mg of ritonavir twice a day and investigator-selected NRTI. Enfuvirtide was optional. The primary intent-to-treat end point was a confirmed HIV RNA viral load of less than 50 copies/mL at week 24 using the US FDA time-to-loss of virologic response algorithm.^{28,29} At week 24, in DUET-1, 170 (56%) patients in the etravirine group and 119 (39%) patients in the placebo group achieved a HIV RNA load of <50 copies/mL ($P = 0.005$). HIV RNA viral load <400 copies/mL was observed in 224 (74%) patients in the etravirine group and in 158 (51%) patients in the placebo group at week 24 ($P = 0.0001$). The mean decline in viral load from baseline in the etravirine group was 2.41 \log_{10} copies/mL compared with 1.70 \log_{10} copies/mL in the placebo group ($P < 0.0001$). In addition, a greater increase in mean CD4 cell count was observed in the etravirine group compared with the placebo group at 89 vs 64 cells/ μ L, respectively ($P = 0.0002$).²⁸ In the DUET-2, by week 24, 183 (62%) patients in the etravirine group and 129 (44%) patients in the placebo group achieved a HIV RNA load of <50 copies/mL ($P = 0.0003$). HIV RNA viral load <400 copies/mL was observed in 221 (75%) patients in the etravirine group and in 159 (54%) patients in the placebo

group at week 24 ($P = 0.0001$). The mean decline in viral load from baseline in the etravirine group was 2.34 \log_{10} copies/mL compared with 1.68 \log_{10} copies/mL in the placebo group ($P < 0.0001$). The mean change in CD4 cell count from baseline was 78 vs 66 cells/ μ L for the etravirine and placebo groups, respectively ($P = 0.36$).²⁹

Pooled 48-week analysis of the DUET studies showed durable virologic efficacy, with significantly more patients in the etravirine arm than in the placebo arm achieving viral load <50 copies/mL (61% vs 40%, respectively; $P < 0.0001$).³⁰ Patients taking etravirine achieved virologic response significantly more quickly than patients taking placebo (median 15.7 and 32.7 weeks for etravirine and placebo, respectively; $P < 0.0001$). The mean 48-week decline in viral load from baseline in the etravirine group was 2.25 \log_{10} copies/mL compared with 1.49 \log_{10} copies/mL in the placebo group ($P < 0.0001$).³⁰ The mean increase in CD4 cell count was significantly higher in the etravirine group compared with the placebo group (98.2 vs 72.9 cells/ μ L, respectively; $P = 0.0006$). In addition, there were fewer AIDS-defining events or death in the etravirine group compared with the placebo group, with 35 (6%) vs 59 (10%) events, respectively ($P = 0.04$).³⁰ Factors found to predict virologic response at 48 weeks were lower baseline viral load, higher CD4 cell count, greater adherence, number of active agents in the background regimen, and less than 3 baseline FC in EC₅₀ to etravirine.

Recently, a phase II, multicenter ANRS 139 TRIO trial evaluated the virologic response to a combination of 3 novel agents among patients on virologic failure with NRTI-, NNRTI-, and PI-resistant HIV. A total of 103 patients were enrolled and treated with raltegravir, darunavir, ritonavir, and etravirine at FDA-approved doses.³⁶ The novel combination was well tolerated, with only 1 patient discontinuing treatment due to adverse events. At week 48, 86% of patients had a HIV RNA viral load of <50 copies/mL and a median CD4 cell count increase of 108 cells/ μ L.³⁶

Safety and tolerability

The 48-week pooled analysis on all 1,203 patients enrolled in DUET-1 and DUET-2 revealed no safety concerns, with the majority of adverse events being grade 1 or 2 in severity. The incidence of grade 3 or 4 adverse events was comparable between the etravirine and the placebo groups, and the mortality in the etravirine group was considered not related to study drug (Table 2).³⁰ Rash was the only adverse event to occur significantly more frequently in the etravirine group compared

Table 2 Adverse events reported in the DUET-1 and DUET-2 studies at week 48³⁰

| Adverse event | ETV + OBT (N = 599) | Placebo + OBT (N = 604) |
|---|------------------------|----------------------------|
| Any adverse event, n (%) | 575 (96) | 580 (96) |
| Grade 3 or 4 adverse event | 199 (33) | 211 (35) |
| Serious adverse events | 118 (20) | 141 (23) |
| Rash (any type) | 115 (19) | 66 (11) |
| Diarrhea | 118 (18) | 142 (24) |
| Nervous system | 103 (17) | 119 (20) |
| Psychiatric | 100 (17) | 118 (20) |
| Nausea | 89 (15) | 77 (13) |
| Headache | 65 (11) | 77 (13) |
| Hepatic | 39 (7) | 37 (6) |
| Adverse events leading to | | |
| Discontinuation | 43 (7) | 34 (6) |
| Deaths | 12 (2) | 20 (3) |
| Selected grade 2–4 laboratory abnormalities | | |
| Triglycerides | | |
| Grade 2 (500–700 mg/dL) | 54 (9) | 43 (7) |
| Grade 3 (751–1200 mg/dL) | 34 (6) | 24 (4) |
| Grade 4 (>1200 mg/dL) | 21 (4) | 11 (2) |
| Pancreatic amylase | | |
| Grade 2 (>1.5–2 × ULN) | 40 (7) | 46 (8) |
| Grade 3 (>2–5 × ULN) | 44 (7) | 51 (8) |
| Grade 4 (>5 × ULN) | 9 (2) | 6 (1) |
| Total cholesterol | | |
| Grade 2 (240–300 mg/dL) | 117 (20) | 101 (17) |
| Grade 3 (>300 mg/dL) | 48 (8) | 32 (5) |
| LDL cholesterol | | |
| Grade 2 (160–190 mg/dL) | 76 (13) | 69 (12) |
| Grade 3 (>190 mg/dL) | 42 (7) | 39 (7) |
| Alanine aminotransferase | | |
| Grade 2 (2.6–5 × ULN) | 37 (6) | 33 (6) |
| Grade 3 (5.1–10 × ULN) | 16 (3) | 10 (2) |
| Grade 4 (>10 × ULN) | 6 (1) | 2 (<1) |
| Aspartate aminotransferase | | |
| Grade 2 (2.6–5 × ULN) | 37 (6) | 49 (8) |
| Grade 3 (5.1–10 × ULN) | 16 (3) | 10 (2) |
| Grade 4 (>10 × ULN) | 3 (<1) | 2 (<1) |

Abbreviations: ETV, etravirine; OBT, optimized background therapy.

with the placebo recipients (19.2% vs 10.9%; $P = 0.0001$). Within the etravirine group, grade 1 or 2 rash occurred in 17.9% and grade 3 in 1.3%, with no grade 4 reported among patients exposed to etravirine. Rash occurred mainly during the second week of therapy with a median time to onset of 14 days (range: 1–472 days). It generally resolved within 2 weeks on continued therapy with a median duration of 15 days (range: 1–402 days). Treatment discontinuation due to etravirine-associated rash occurred in 2.2% of patients.³⁰ The incidence of etravirine-associated rash was higher in women than in men (30% vs 18%; $P = 0.03$). Patients with a history of NNRTI-related rash did not appear to have a higher risk for developing etravirine-related rash compared with patients

with no history of NNRTI-related rash (22% vs 19%, respectively). There was no association between baseline CD4 cell count and etravirine-associated rash regardless of sex. The overall incidence of neuropsychiatric disorders was low, and disorders were mostly grade 1 or 2 events and comparable between the etravirine and placebo groups. The incidence of hepatic adverse events and laboratory abnormalities, including hepatic and lipid parameters, were mostly grade 1 or 2 in severity and comparable between the etravirine and the placebo groups (Table 2).³⁰

Etravirine resistance

Etravirine-resistance-associated mutations (RAM) have been characterized both *in vitro* and *in vivo*.^{14,37} Unlike the first-generation NNRTIs, etravirine requires multiple mutations for the development of resistance (Table 3).³⁷ The impact of baseline genotype on virologic response to etravirine among subjects failing first-generation NNRTI was investigated in the DUET-1 and DUET-2 trials.^{28,29} Of the 44 NNRTI RAM, 13 mutations were initially identified by their association, with at least a 25% decline in response to etravirine compared with a subgroup of patients with no detectable NNRTI RAM at baseline.³⁸ Recently, further analysis of the pooled DUET-1 and DUET-2 data has expanded the number of etravirine RAM to 17, with Y181C and G190A being the most prevalent at baseline and present in 32% and 23.3% of patients, respectively, enrolled in the DUET studies (Table 3).³⁹ The genotypic and phenotypic correlates of virologic response to etravirine defined as a HIV RNA load <50 copies/mL at 24 weeks were examined by the pooled analysis of the DUET-1 and DUET-2 trials. A weighted genotypic score was developed by assigning a relative weight factor to each etravirine RAM according to its impact on virologic response and FC in the EC₅₀. The relative weight factors were determined with random forest and linear modeling techniques, using matching genotypic and phenotypic data with virologic outcomes from the DUET trials and from a panel of NNRTI-resistant, recombinant HIV-1 clinical isolates.³⁷ Among the 17 etravirine RAMs, the highest weight factor was assigned to Y181I and Y181V, with a weight factor of 3, followed by K101P, L100I, Y181C, and M230L, with a weight factor of 2.5 (Table 3). Etravirine-weighted genotypic score was graded as highest virologic response associated with the lowest score of 0–2, intermediate virologic response of 2.5–3.5, and reduced virologic response of ≥ 4 , and correlated with virologic suppression at 24 weeks in 74.4%, 52% and 37.7% of patients, respectively (Table 4).³⁷ The effect of baseline etravirine FC

Table 3 Genotype weight factor and FC in EC₅₀ of etravirine-resistance-associated mutations³⁷

| Etravirine RAM | Genotype weight factor | Etravirine FC in EC ₅₀ in HIV-1 clinical isolates | | Etravirine FC in EC ₅₀ in a single SDM |
|--------------------|------------------------|--|-----|---|
| | | Median | n | |
| Y181I | 3.0 | 42.0 | 34 | 12.5 |
| Y181V | 3.0 | 10.4 | 28 | 17.4 |
| K101P | 2.5 | 22.3 | 65 | 6.2 |
| L100I | 2.5 | 6.7 | 264 | 1.8 |
| Y181C | 2.5 | 4.4 | 552 | 3.9 |
| M230L | 2.5 | 4.3 | 20 | 3.4 |
| E138A | 1.5 | 2.9 | 44 | 2.0 |
| V106I | 1.5 | 2.6 | 63 | NA |
| G190S | 1.5 | 0.8 | 32 | 0.2 |
| V179F ^a | 1.5 | NA | 0 | 0.1 |
| V90I | 1.0 | 2.0 | 97 | 1.5 |
| V179D | 1.0 | 1.7 | 33 | 2.6 |
| K101E | 1.0 | 1.5 | 24 | 1.7 |
| K101H | 1.0 | 1.1 | 8 | 1.3 |
| A98G | 1.0 | 1.0 | 127 | 2.5 |
| V179T | 1.0 | 0.9 | 2 | 0.8 |
| G190A | 1.0 | 0.8 | 226 | 0.8 |

^aV179F when present was always associated with Y181C.

Abbreviations: EC₅₀, 50% effective concentration; RAM, resistance-associated mutations; FC, fold change; SDM, site directed mutant.

in EC₅₀ on virologic suppression at week 24 was evaluated by analysis of covariance to determine the clinical cut-off values. The EC₅₀ was derived from the Virco phenotype assay (Antivirogram[®]; Virco BVBA, Mechelen, Belgium). Patients with a baseline etravirine FC in EC₅₀ of 3 or less had the highest virologic response (70.6%) (Table 4).³⁷ Patients with intermediate response (50% virologic suppression) had an etravirine EC₅₀ FC of >3 to ≤13, and patients with an etravirine EC₅₀ FC of >13 had reduced response, with virologic suppression in only 36.7% of patients (Table 4).³⁷

An alternate analysis of biological and clinical cut-off values was performed by Coakley et al on 199 baseline samples using the PhenoSense™ HIV (Monogram Biosciences, San Francisco, California, USA).⁴⁰ The lower clinical cut-off value for etravirine was defined as the FC above which HIV RNA response was first observed to decline relative to the reference population. Virologic outcomes were evaluated on the DUET studies at weeks 2, 4, 8, and 24 in relation to baseline etravirine FC. The biological cut-off was defined

as the ninety-ninth percentile of etravirine FC values from 1,693 viral isolates without mutations conferring resistance to NRTIs, NNRTIs, or PIs.⁴⁰ In a model adjusted for the activity of the background therapy, the activity of etravirine was observed to be reduced at a FC > 2.9. Further studies from the same group, using the lower clinical cut-off value of 2.9 FC to define reduced susceptibility, correlated a novel etravirine RAM weighting score with the relative impact on etravirine susceptibility in which a score of 4 or more defined reduced susceptibility.⁴¹ Mutations with a score of 4 were L100I, K101P, and Y181C/I/V. A score of 3 was assigned to E138A/G, V179E, G190Q, M230L, and K238N. A score of 2 was assigned to K101E, V106A/I, E138K, V179L, Y188L, and G190S. A score of 1 was assigned to V90I, K101H, V106M, E138Q, V179D/F/M, Y181F, V189I, G190E/T, H221Y, P225H, and K238T.^{41,42} Contrary to the first-generation NNRTIs, the etravirine resistance patterns are more complex and continue to evolve. Recently, the combination of Y181C with N348I and 399D mutations, not included among

Table 4 Relationship between genotypic and phenotypic susceptibility categories using the etravirine-weighted genotypic score³⁷

| | Patients, n (%) | Baseline etravirine fold change in EC ₅₀ , n (%) | | |
|-------------------------------------|-----------------|---|---------------|-----------|
| | | ≤3 (S) | >3 to ≤13 (I) | >13 (R) |
| Etravirine-weighted genotypic score | | | | |
| 0–2 (S) | 225 (55.8) | 208 (92.4) | 16 (7.1) | 1 (0.4) |
| 2.5–3.5 (I) | 101 (25.1) | 42 (41.6) | 31 (30.7) | 28 (27.7) |
| >4 (R) | 77 (19.1) | 19 (24.7) | 27 (35.1) | 31 (40.3) |

Abbreviations: EC₅₀, 50% effective concentration; S, susceptible; I, intermediate; R, resistant.

the etravirine RAM, caused a 6.4- to 12.6-fold reduction in etravirine susceptibility.^{43,44}

Patient perspective and conclusion

Etravirine, a second-generation NNRTI, received FDA approval in January 2008 for the management of treatment-experienced, HIV-infected adults with NNRTI-resistant viruses. It has a high genetic barrier to resistance and is active against nevirapine- and efavirenz-resistant viruses. Etravirine is safe and well tolerated, it does not have the neuropsychiatric or hepatic side effects of efavirenz or nevirapine, and its safety profile is comparable to placebo with the exception of rash. Rash was grade 1 or 2 in the great majority of patients and was self-limited. History of NNRTI-related rash was not a predisposing factor. Etravirine is a pregnancy category B drug; its safety, pharmacokinetic profile, and efficacy have not been studied in pregnant women. Pediatric phase I/II studies are being conducted, and preliminary data suggest that it is safe and well tolerated. Pharmacokinetic studies in children between 6 and 17 years have shown that a dose of 5.2 mg/kg twice a day leads to exposure comparable to exposure by the adult dose of 200 mg twice a day.⁴⁵ In the DUET-1 and DUET-2 phase III efficacy trials, etravirine was always used in combination with ritonavir-boosted darunavir, a PI with antiviral activity in PI treatment-experienced patients. With the recent FDA approval of darunavir, raltegravir, and etravirine (and maraviroc for CCR5 tropic viruses), all with antiviral activity against multiple-drug-resistant HIV isolates, it is now possible for treatment-experienced patients to aim for virologic suppression comparable to treatment-naive patients as has been shown in the TRIO trial.³⁶ In this trial, 86% of patients with multiple-drug-resistant HIV treated with raltegravir-, etravirine-, and ritonavir-boosted darunavir had a HIV RNA load of <50 copies/mL at 48 weeks.³⁶

In addition to the virologic efficacy, analysis from the DUET trials has shown a significant reduction in the hospitalization rate and in the number of hospitalization days among patients enrolled in the etravirine arm compared with the placebo arm.⁴⁶ Ongoing studies on the pharmacokinetic interaction with newer agents; the safety, tolerability, and pharmacokinetic studies in children; and the prospect of once-a-day regimen due to the long half-life are subject to investigation.

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Disclosures

The author reports no conflicts of interest in this work.

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