Combating Non-nucleoside Reverse Transcriptase Inhibitor Resistance with a Focus On Etravirine (Intelen) for HIV-1 Infection

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INTRODUCTION

Many aggressive approaches, such as highly active antiretroviral therapies (HAART), are available for the treatment of human immunodeficiency virus type-1 (HIV-1) infection. To date, six classes of antiretroviral drugs are available for use in combination therapy:1

- nucleoside reverse transcriptase inhibitors (NRTIs)
- non-nucleoside reverse transcriptase inhibitors (NNRTIs)
- protease inhibitors (PIs)
- fusion inhibitors
- cellular chemokine receptor-5 (CCR-5) antagonists
- integrase inhibitors

Antiretroviral drugs are used to inhibit viral replication and thus reduce the viral load in the blood. Although therapeutic drug regimens for treating HIV-1 infection are quite complex and costly, they are very efficacious in inhibiting viral replication. The goal of HIV treatment is to achieve the greatest suppression of symptoms while maximizing quality of life for these patients.

The addition of the NNRTI class of drugs has become an important element in HAART. NNRTIs bind directly to the enzyme reverse transcriptase, which prevents the conversion of RNA to DNA. The selection of a NNRTI drug regimen for individuals infected with HIV-1 is now limited to a single line of therapy as a result of resistance to all first-generation NNRTIs such as efavirenz (Sustiva, Bristol-Myers Squibb), nevirapine (Viramune, Boehringer Ingelheim), and delavirdine (Rescriptor, Pfizer).2 Drug resistance makes therapy selection quite intricate and is a major reason for HAART failure.

Over the previous few years, studies have heightened concerns about frequent transmission of NNRTI-resistant isolates. Resistance to this drug class occurs when the virus begins to develop mutations that prevent NNRTIs from binding to the reverse transcriptase enzyme; this inhibition then results in loss of efficacy.3 Approximately 20% of newly reported cases of infected patients were found to harbor HIV-1 with reduced susceptibility to NNRTIs. The use of currently available NNRTIs in treatment-experienced patients is limited because of possible cross-resistance of a single amino-acid substitution in HIV-1 reverse transcriptase.4

On January 18, 2008, the Food and Drug Administration (FDA) granted accelerated approval for etravirine (Intelen [TMC125], Tibotec, a division of Ortho-Biotech). This innovative antiretroviral drug gained its approval based on the 24-week analysis of HIV viral loads and CD4 counts from two randomized, double-blind, placebo-controlled phase 3 trials: DUET-1 (TMC125, Study C206) and DUET-2 (TMC125, Study C216).2

Etravirine is the first drug in the second generation of NNRTIs with activity against NNRTI-resistant HIV-1. It has an immense advantage over other NNRTIs because it exhibits compelling in vitro activity against HIV-1 NNRTI-naive and NNRTI resistance–associated mutations (RAMs). Etravirine is efficacious against most strains that are resistant to the other NNRTIs, and this unique property differentiates it from other drugs in its class. Etravirine has in vitro activity against both wild-type and NNRTI-resistant HIV strains,4,5 and it can be used in combination with other antiretroviral agents to treat HIV infection.6

CHEMISTRY AND PHARMACOLOGY

A diaryl pyrimidine, etravirine is the first new NNRTI to be introduced in nearly 10 years.6 It works by blocking HIV’s reverse transcriptase enzyme. After the HIV genetic material is deposited inside a cell, its RNA must be converted (reverse-transcribed) into DNA. NNRTIs inhibit this process and prevent the virus from infecting the CD4 cell and from producing new virus particles.2,3,5

The chemical structure of etravirine is 4-[(6-amino-5-bromo-2-(4-cyanophenyl) amino)-4-pyrimidinyl]oxy]-3,5-dimethylbenzonitrile. The flexibility of the chemical molecule allows it to continually bind to the reverse transcriptase enzyme that has become resistant to other NNRTIs. Etravirine also demonstrates increased binding affinity to reverse transcriptase despite binding-site changes induced by the presence of common NNRTI-resistant mutations. Etravirine is practically insoluble in water over a wide pH range, but it is soluble in polyethylene glycol (PEG) 400.6

PHARMACOKINETICS

All patients in phase 3 clinical trials received darunavir/ritonavir (Prezista, Tibotec/Norvir, Abbott) 600/100 mg twice daily as part of the background regimen. Because the systemic exposure of etravirine is decreased by about 50%...
when it is taken under fasting conditions, etravirine should always be administered with food. The absorption of etravirine is not affected by the coadministration of oral ranitidine (Zantac, GlaxoSmithKline) or omeprazole (e.g., Prilosec, AstraZeneca) in healthy patients. It is 99% bound to plasma proteins, primarily albumin and alpha-acid glycoprotein. Distribution through other plasma compartments, such as the cerebrospinal fluid and genital tract secretions, have not been evaluated in clinical trials.

Etravirine is metabolized primarily hepatically through cytochrome CYP 450 3A4, CYP 2C9, and CYP 2C19 enzymes. In clinical trials, clearance for etravirine was reduced in HIV-1 patients with hepatitis B or C; however, no dosage adjustment is necessary. Elimination occurs mainly via the feces (93.7%), with small amounts of the drug excreted in the urine (1.2%). The mean elimination half-life of etravirine is 41 (±20) hours after steady state.

Although several clinical trials involving etravirine are ongoing, the agent’s pharmacokinetic parameters have not been established in children or treatment-naive adults. No significant differences in pharmacokinetics in terms of race, sex, or age have been demonstrated in patients 18 to 77 years of age.4,5

**DRUG RESISTANCE**

Etravirine’s activity against resistant strains is strongly affected by the number of NNRTI mutations present as well as by the specific mutations. It is critical to discontinue the first-generation NNRTI that has demonstrated resistance in order to avoid any further resistance that would diminish the efficacy of etravirine. The presence of three or more NNRTI mutations sharply diminishes the response to etravirine regimens. These mutations are Val90lle, Ala98Gly, Leu100le, Lys101Glu, Lys101Pro, Val106lle, Val179Asp, Val179Phe, Tyr181Cys, Tyr181lle, Tyr181Val, Gly190Ala, and Gly190Ser. The presence of the most common mutations (K103N and Y181C) did not affect the treatment response in patients receiving etravirine in the DUET studies.4,6

**CLINICAL TRIALS**

In November 2006, Tibotec Pharmaceuticals launched clinical trials to study the potential use of etravirine in treatment-experienced HIV-1 patients. Based on the findings, etravirine was approved in 2008. DUET-1 and DUET-2 were randomized, double-blind, placebo-controlled phase 3 trials that were conducted to compare the therapeutic outcomes of etravirine plus a background regimen against placebo in combination with a background regimen. The investigators also sought to distinguish which patients had reused or who did not use enfuvirtide (Fuzeon, Roche).

Participants included HIV-1-infected patients who were at least 18 years of age with a viral load of more than 5,000 copies/mL, who were receiving stable antiretroviral therapy for at least eight weeks, and who had a minimum of one confirmed NNRTI resistance–associated mutation.

DUET-1 and DUET-2 were indistinguishable from one another, but they were performed in treatment-experienced HIV-1 patients with documented evidence of NNRTI and PI resistance in different regions.4,5

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**Table 1 Baseline Characteristics: DUET-1 and DUET-2 Pooled Analysis**

<table>
<thead>
<tr>
<th></th>
<th>Etravirine + BR (n = 599)</th>
<th>Placebo + BR (n = 604)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median viral load (log10 copies/mL)</td>
<td>4.8</td>
<td>4.8</td>
</tr>
<tr>
<td>Median CD4+ (cells/mm3)</td>
<td>99</td>
<td>109</td>
</tr>
<tr>
<td>Previous NNRTI use ≥1 (%)</td>
<td>91.8</td>
<td>92.1</td>
</tr>
<tr>
<td>Median NNRTI RAMs (range)</td>
<td>2 (0–5)</td>
<td>2 (0–4)</td>
</tr>
<tr>
<td>Previous enfuvirtide use (%)</td>
<td>39.6</td>
<td>41.9</td>
</tr>
</tbody>
</table>

BR = background regimen; NNRTI = non-nucleoside reverse transcriptase inhibitor; RAMs = resistance-associated mutations.

From etravirine (Intelence), package insert, January 2008.

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**The DUET-1 Trial**

Clinical data were collected between November 10, 2005, and July 18, 2006. DUET-1 included 615 participants from Argentina, Brazil, Chile, France, Mexico, Panama, Puerto Rico, Thailand, and the U.S. who were randomly assigned, in a 1:1 ratio, to receive TMC125 (etravirine) (n = 304) or placebo (n = 308). Participants received either 200 mg of etravirine or placebo as a twice-daily drug regimen. The investigator selected a background regimen that included an NRTI and optional enfuvirtide. All patients were to receive darunavir 600 mg with ritonavir 100 mg twice daily as a background antiretroviral regimen. The NRTI agent was selected and administered according to virus genotype resistance at screening.

A total of 70 participants (42 in the etravirine group, 56 in the placebo group) discontinued treatment because of virological failure, defined as a viral load reduction of less than 0.5 log10 copies/mL from baseline at the eighth week or less than 1.0 log10 copies/mL at week 12. Analyses were by intention to treat.

The primary endpoint—obtaining a confirmed viral load of less than 50 copies/mL at week 24—was reached by 170 etravirine patients (56%) and by 119 placebo participants (39%). Overall, achievement of a secondary endpoint—obtaining a confirmed viral load of less than 400 copies/mL, a change in viral load from baseline, a change in CD4 cell count from baseline, and safety and tolerability—was greater with etravirine than with placebo.

Regardless of the amount of additional active agents received, 224 patients taking etravirine (74%) and 158 patients taking placebo (51%) achieved a viral load of less than 400 copies/mL at week 24. Twenty-one etravirine patients (47%) and four placebo patients (9%) achieved a viral load of less than 50 copies/mL without any additional active agents in the background regimens. The etravirine group reported a mean change in viral load of –2.41 log10 copies/mL from baseline (standard deviation [SD], 1.28), whereas the placebo group reported only –1.70 log10 copies/mL (SD, 1.49).

According to the data, the etravirine patients attained a greater increase in CD4 count at an average of 89 (93.65)
cells/mm\(^3\), compared with the placebo group, which had an average of 64 (91.41) cells/mm\(^3\). During the study, a total of 12 category C AIDS-defining illnesses or deaths occurred, as defined by the Centers for Disease Control and Prevention (CDC); eight patients (3%) had received etravirine and 21 patients (7%) received placebo.\(^4\)

### The DUET-2 Trial

DUET-2 also involved treatment-experienced patients with infection that was resistant to NNRTI therapy. This study was designed to compare the extended efficacy, safety, and tolerability of etravirine and placebo for up to 96 weeks. Data were collected in 12 centers in 12 countries (Australia, Belgium, Canada, France, Germany, Italy, Netherlands, Poland, Portugal, Spain, United Kingdom, and the U.S.). This study enrolled 593 participants who were randomly assigned to treatment; however, two patients withdrew before therapy began.

Data for 591 patients were collected until January 18, 2007, after at least 24 weeks of treatment. Fifty-one etravirine patients (17%) and 73 placebo patients (25%) withdrew from the study because of virological failure. Baseline measurements revealed that 382 patients (65%) had two or more NNRTI resistance-associated mutations and 533 patients (90%) had four or more NNRTI resistance--associated mutations. The baseline evaluation for primary PI mutations showed that 387 (66%) patients had four or more mutations and 261 (44%) had three or more darunavir resistance--associated mutations.

The data that were collected during this extended trial clearly revealed that the etravirine group attained better virological responses than the placebo group. At week 24, the etravirine patients far surpassed the placebo patients in achieving a confirmed viral load of less than 50 copies/mL, less than 400 copies/mL, and a mean change in viral load. The etravirine patients had better response rates to therapy regardless of their baseline viral load.\(^3\)

### ADVERSE DRUG EVENTS

Although HAART remains the standard of care for HIV-1 infection, it is also associated with numerous adverse drug effects (ADEs). During the DUET-1 treatment period, 282 participants (93%) receiving etravirine and 287 participants (93%) receiving placebo reported at least one ADE. The most common ADEs occurring in 10% or more of patients in either group included rash, nausea, diarrhea, and headache. Fatigue, abdominal pain, hypertension, pneumonia, and peripheral neuropathy were noted in 1% or more of patients in either group. The development of any type of rash was documented in 61 etravirine patients (20%) and in 30 placebo patients (10%). Rash occurred more frequently with etravirine than with placebo (16.9% vs. 9.3%, respectively), as did nausea (13.9% vs. 11.1%, respectively). Serious skin reactions such as Stevens–Johnson syndrome and erythema multiforme were reported during this study.

ADEs resulted in an equal number of patients (i.e., 16 participants [5%]) from both the etravirine and placebo groups discontinuing treatment. ADE-related deaths included four etravirine patients and eight placebo patients who had started therapy during the treatment period. None of the deaths was caused as a result of any single therapeutic component of etravirine.

Laboratory parameters did not reveal clinically significant differences between etravirine and placebo. When compared with placebo, etravirine did not illustrate any applicable outcome in terms of lipid concentrations, including triglycerides. Abnormal grade 3 and 4 laboratory values associated with lipid, hepatic, and pancreatic levels were equivalent in both treatment groups.\(^4\)

### DRUG INTERACTIONS AND CONTRAINDICATIONS

Although there were no known contraindications with etravirine at the time of the FDA’s approval,\(^6\) a number of medications are not currently recommended for use with etravirine as a result of drug interactions.\(^7\) Etravirine is a substrate of the CYP 3A4, CYP 2C9, and CYP 2C19 enzymes; an inducer of CYP 3A4; and an inhibitor of CYP 2C9 and CYP 2C19.

Many significant interactions may occur when additional drugs are taken in combination with other antiretroviral agents.

Serum concentrations of atazanavir (Reyataz, Bristol-Myers Squibb), maraviroc (Selzentry, Pfizer), and raltegravir (Isentress, Merck) are decreased when they are taken concomitantly with etravirine. Etravirine increases the serum concentration of fosamprenavir (Lexiva, GlaxoSmithKline) when both agents are used simultaneously. Etravirine levels are considerably decreased when used with tipranavir, full-dose ritonavir (Norvir), efavirenz (Sustiva), and nevirapine (Viramune). Moderate levels of etravirine are decreased with saquinavir (Inverase, Roche), darunavir (Prezista), and tenofovir (Viread, Gilead). Etravirine concentrations are increased by lopinavir/ritonavir (Kaletra, Abbott) and delavirdine (Rescriptor). Because of the large elevation in etravirine levels with the concomitant use of Kaletra, etravirine should be prescribed with caution.\(^6,7\)

Etravirine should not be administered with other NNRTIs, unboosted PIs, atazanavir/ritonavir, fosamprenavir/ritonavir, or tipranavir/ritonavir. Close monitoring and dosage adjustments are required when interacting antiretroviral agents are included in the patient’s regimen.\(^6\)

Drug interactions also exist between etravirine and other non-HAART medications. Because of the litany of drug interactions that may occur, the patient’s complete medication profile should be reviewed before etravirine treatment begins. The concentrations of some antiarrhythmic medications, such as bepridil (Vascor, Ortho-McNeil), amiodarone continued on page 491
(Cordarone, Wyeth), and quinidine (e.g., Quinora), may be decreased with co-administration of etravirine. Because warfarin (Coumadin, Bristol-Myers Squibb) concentrations may be increased with etravirine, the International Normalized Ratio (INR) should be closely monitored in these patients.

Common inducers of the CYP 450 enzymes, such as carbamazepine (Tegegrelot, Novartis), phenobarbital, and phenytoin (Dilantin, Pfizer) may cause decreased plasma concentrations of etravirine, resulting in a possible loss of therapeutic effect. Because of the loss in efficacy, drug combinations with CYP 450 enzyme inducers should be avoided.

Etravirine can also interact with medications used to treat mycobacterial infections and tuberculosis. Clarithromycin (Biaxin, Abbott), rifampin (Rifadin, Aventis) and rifabutin (Mycobutin, Pfizer) can decrease etravirine concentrations. Agents used to treat thrush, such as fluconazole (Diflucan, Pfizer), ketoconazole (Nizoral, Janssen), itraconazole (Sporanox, PriCara/Janssen/Ortho-McNeil), and voriconazole (Vfend, Pfizer) may require dosage adjustments when used in combination with etravirine.

Patients should be advised to avoid over-the-counter herbal medications without the consent of their doctor. The concomitant use of etravirine and St. John’s wort, for instance, can result in decreased plasma concentrations of etravirine. Statins that can be administered with etravirine without any need for dosage adjustments include atorvastatin (Lipitor, Pfizer) fluvastatin (Lescol, Novartis), pravastatin (Pravachol, Bristol-Myers Squibb), and rosuvastatin (Crestor, Astra Zeneca). All patients should be advised to consult their doctor or pharmacist before adding any drug to their regimen while taking etravirine.6,7

**PREGNANCY CATEGORY**

The FDA has classified etravirine as a Pregnancy Category B medication. In animal studies, a dose of 400 mg/day (the normal adult dose) provided no evidence of harm to the fetus. Etravirine should not be used in pregnancy unless the benefits outweigh the risks to the fetus. The CDC recommends that all HIV-infected mothers avoid breast-feeding to reduce the risk of passing the virus on to the newborn.6

**COST**

In the U.S., the average wholesale price (AWP) of etravirine 200 mg (two 100-mg tablets) twice daily is $798 for a one-month supply. The AWPs for a month’s supply of the approved first-generation NNRTIs are $598 for efavirenz (Sustiva) and $393 for nevirapine (Viramune).6

**CONCLUSION**

Innovation in HIV therapy was once considered to be at a standstill, and it was thought that there would be no further scientific or economic incentives for future progress. Newly approved drugs such as etravirine have dispelled this myth and have proved to be effective and well tolerated.6

Viral replication and HIV-1-resistant strains raise great concern among treatment-experienced patients. Patients receiving HAART are finding few treatment options as gene mutations continue to develop. The NNRTI class plays a vital part in HIV-1 therapy; nevertheless, resistance can quickly develop after therapy begins.

Etravirine is the first second-generation NNRTI that has proved efficacious in treating highly resistant HIV infection. Etravirine’s mechanism of action differs from that of other drugs in its class. Its molecular flexibility allows it to bind to reverse transcriptase in multiple conformations. Even when mutations are present, etravirine can exert activity toward the enzymes.

New clinical trials are in the process of recruiting participants for further studies to test the safety and efficacy of etravirine in treatment-naive adults and pediatric patients. Etravirine’s availability in the U.S. offers patients a second chance at using NNRTIs in their drug regimens.

**REFERENCES**


